Nitric oxide, oxygen, and prostacyclin in children with pulmonary hypertension

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Abstract

Objective—To test the vasodilatory response of the pulmonary vascular bed in children with pulmonary hypertension.

Design—Prospective dose response study in which the effects of inhaled nitric oxide (NO) are compared with those of oxygen and intravenous prostacyclin.

Patients and interventions—The vasodilator test was performed in 20 patients in whom mean pulmonary artery pressure (PAPm) was ≥ 40 mm Hg and/or pulmonary vascular resistance index was ≥ 4 Um². Haemodynamic effects of inhaled NO (20, 40, and 80 ppm) at a fractional inspired oxygen (FiO₂) value of 0.3, pure oxygen, oxygen at FiO₂ 0.9–1.0 combined with NO as above or with intravenous prostacyclin at 10 and 20 ng/kg/min were measured.

Result—NO decreased PAPm with a dose response from 20 to 40 ppm (mean change at 40 ppm -5.50 , 95% confidence interval (CI) -7.98 to -3.02 mm Hg). Maximal decrease in the ratio of pulmonary to systemic vascular resistance was achieved with a combination of NO 80 ppm and oxygen (-0.18 , 95% CI -0.26 to -0.10). Increase in the pulmonary flow index was greatest with pure oxygen in those with an intracardiac shunt (8.52, 95% CI -0.15 to 17.20 l/min/m²). Neither NO nor oxygen altered systemic arterial pressure but intravenous prostacyclin lowered systemic arterial pressure and resistance.

Conclusions—NO selectively reduces pulmonary vascular resistance and pressure maximally at 40 ppm. Oxygen reduces pulmonary vascular resistance and NO potentiates this reduction without affecting the systemic circulation. Prostacyclin vasodilates the pulmonary and the systemic circulations.

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Keywords: pulmonary hypertension; nitric oxide; prostacyclin; congenital heart disease; children

Pulmonary circulation is an important determinant of the operability of patients with congenital heart defects.¹ Raised pulmonary vascular pressure and resistance are usually secondary to intracardiac shunts but may occasionally be raised primarily or as a result of non-cardiac disease. The risks of cardiac surgery in patients with congenital heart disease increase with pulmonary hypertension. Reactivity to vasodilators in patients with primary pulmonary hypertension correlates

with improved survival.² In patients for whom the only surgical option is lung or heart lung transplantation, vasodilator testing may be useful to identify those requiring urgent operation. Several vasodilating agents, such as oxygen, tolazoline, and prostacyclin, have been used to test the vasoreactivity of the pulmonary circulation.³ These drugs, however, are not selective pulmonary vasodilators, thereby making interpretation difficult.

Undamaged arterial endothelial cells continuously secrete nitric oxide (NO), which, as an inhalant, seems to be an ideal selective pulmonary vasodilating agent.^{4–17} It is almost immediately inactivated by exposure to haemoglobin.¹⁸ Thus it affects only the pulmonary vascular bed, which it reaches from lung alveoli, without blood contact. The aim of our study was to compare the pulmonary vasodilator effects of inhaled NO with those of oxygen, and correspondingly, to assess the maximal vasodilatory capacity achieved with a combination of high oxygen concentration and either inhaled NO or intravenously administered prostacyclin.

Patients and methods

PATIENTS

Ethical approval was obtained from the institutional review board of the children's hospital. Written informed consent was obtained from the patients' parents. Patients (age range from 0.3 to 15.6 years) had greatly raised pulmonary vascular resistance—that is, their pulmonary vascular resistance index (PVRI) was ≥ 4 Wood's units $\times$ m² and/or their mean pulmonary artery pressure (PAPm) was > 40 mm Hg. Cardiac catheterisation was performed in 28 children with primary ($n = 2$) or secondary ($n = 26$) pulmonary hypertension. Secondary pulmonary hypertension was a consequence of intracardiac shunts ($n = 24$), vasculitis ($n = 1$), or bronchopulmonary dysplasia and high altitude exposure ($n = 1$). Eight patients were excluded: four with left heart obstruction, two with persistent hypercapnia (one with tracheobronchomalacia and another with pulmonary atelectases), one because of technical problems in monitoring NO and nitric dioxide (NO₂) concentrations, and one because of pulmonary hypertensive crisis during the study. One patient who had bronchopulmonary dysplasia and high altitude exposure and a PVRI of 3.8 Um² and PAPm of 19 mm Hg was included because the decision to treat with vasodilators was dependent on the responsiveness to studied vasodilators.

Sixteen of the 20 patients studied had a congenital heart defect with left to right shunting. Ten patients with a congenital heart defect had

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Table 1 Patient data

Age (years)/ sex	Diagnosis	Tris. 21	Mean pulmonary artery pressure (mm Hg)			Pulmonary vascular resistance index (Umr ²)					
			FiO ₂ =0.3	NO 40 FiO ₂ =0.3	PGI ₂ 20 FiO ₂ >0.9	FiO ₂ =0.3	NO 40 FiO ₂ =0.3	FiO ₂ >0.9	NO 40 FiO ₂ >0.9	PGI ₂ 20 FiO ₂ >0.9	
Congenital heart disease											
1	0.3/F	ASD VSD	No	48	44	42	4.3	3.3	1.6	1.3	1.4
2	0.3/M	VSD DORV	No	55	45	44	2.8	2.4	0.6	0.8	0.7
3	0.3/F	Truncus arteriosus	No	50	37	57	6.8	2.7	1.4	1.2	1.8
4	0.4/M	ASD VSD	No	39	33	25	3.8	3.3	2.7	2.9	1.6
5	0.4/F	AVSD	Yes	50	40	34	6.5	4.5	2.6	3.0	3.1
6	0.4/M	ASD VSD PDA	Yes	61	57	66	7.3	8.1	6.5	6.2	9.5
7	0.4/F	VSD PDA	Yes	64	71	53	7.7	7.8	3.5	7.5	2.4
8	0.5/F	VSD PDA	Yes	41	37	30	2.9	2.8	2.9	2.3	1.6
9	0.6/F	AVSD	Yes	39	37	31	5.5	4.8	1.2	1.2	0.8
10	0.8/F	VSD	Yes	41	36	32	2.9	2.8	2.6	1.6	1.4
11	1.1/M	ASD VSD PDA	Yes	43	39	47	5.4	4.0	2.9	2.8	2.6
12	3.0/F	Multiple VSDs	Yes	55	51	56	16	11.9	3.6	9.3	8.4
13	4.0/M	AOP window	No	62	61	66	4.9	3.5	3.4	3.8	5.4
14	7.2/M	Postop hemitruncus and VSD	No	57	38	36	8.1	6.3	5.1	5.1	5.9
15	12.8/F	VSD	Yes	54	52	45	8.9	10.0	7.7	6.7	6.7
16	13.6/F	VSD PDA	Yes	77	80	76	18.1	17.3	11.6	13.0	10.1
Mean	2.9			52	47	46	7.0	6.0	3.7	4.3	4.0
Other causes of pulmonary hypertension											
17	1.1/F	BPD HAE PH	No	19	18	23	3.8	3.7	3.2	1.8	2.1
18	2.6/F	PPH	No	64	65	67	18.9	18.8	14.2	14.3	12.3
19	12.9/M	PPH	No	127	125	115	35.1	29.0	29.2	24.5	25.6
20	15.6/F	SLE PH	No	29	24	37	12.2	7.4	9.4	8.4	6.3
Mean	8.1			60	58	61	17.5	14.7	14.0	12.3	11.6

AOP window, aortopulmonary window; ASD, atrial septal defect; AVSD, atrioventricular septal defect; BPD, bronchopulmonary dysplasia; DORV, double outlet of right ventricle; HAE, high altitude exposure; PDA, patent ductus arteriosus; PH, pulmonary hypertension; PPH, primary pulmonary hypertension; SLE, systemic lupus erythematosus; VSD, ventricular septal defect.

trisomy 21. Table 1 shows patient data and basic pulmonary measurements.

HAEMODYNAMIC ASSESSMENT

Oxygen consumption was measured before and immediately after catheterisation with a metabolic monitor (Deltatrac; Datex, Engström, Helsinki, Finland). Patients were sedated by a standardised method during catheterisation (ketamine infusion supplemented with fentanyl or isoflurane boluses, or both). Mechanical ventilation with a volume controlled ventilator (Servo; Siemens, Stockholm, Sweden) was used in 17 patients. Endotracheal intubation was facilitated with pancuronium bromide. Three patients were not intubated. The end tidal carbon dioxide concentration was monitored with a capnometer (Datex). Systemic artery pressure was measured non-invasively with a manometer in the upper right arm (Dinamap; Critikon, Tampa, Florida, USA or Symphony N-3000; Nellcor, Pleasanton, California, USA), but also in the radial artery in 18 patients. Heart rate, arterial and venous oxygen saturation, blood gas tension, systemic arterial and venous pressure, and ventricular pressure were recorded at the start of the study. Pulmonary artery pressure and left ventricular end diastolic pressure (14 patients) or pulmonary capillary wedge pressure (six patients) were measured to assess the transpulmonary gradient. Oxygen consumption, measured according to Fick's principle, was used to calculate pulmonary and systemic blood flow.

PROTOCOL FOR THE VASODILATOR TEST

NO (1000 ppm) in nitrogen was administered through a separate flow meter and mixed with air and oxygen near the endotracheal tube or face mask. Inhaled NO and NO₂ concentrations were measured endotracheally in intu-

bated patients (n = 17) or in the nasopharynx using the electrochemical method (Polytron; Dräger, Germany) (n = 3). Arterial and venous saturation and methaemoglobin (metHb) concentration (IL CO-Oximeter 482; Instrumentation Laboratory, Lexington, Massachusetts, USA) were determined.

Response of the pulmonary vascular bed to various vasodilator drugs was tested serially. Before each change there was a washout period of five minutes during which the patient breathed a basic gas mixture: oxygen (30%) in nitrogen (70%) during the first stage and pure oxygen during the second. In the first stage after baseline measurements NO (20 ppm) was added to inspired gas for five minutes and haemodynamic measurements were repeated at the end of the period. NO inhalation was repeated at doses of 40 and 80 ppm. During the second stage the inhaled oxygen concentration was increased to 100% for 10 minutes and thereafter NO inhalation was repeated at doses of 20, 40, and 80 ppm for five minutes with pauses of equal length.

The combined effect of high oxygen concentration and prostacyclin (Flolan; Wellcome, London, UK) at doses of 10 and 20 ng/kg/min was measured after 10 minutes. Because prostacyclin has a half life of several hours, this vasodilator was given at the end of the protocol and there was no interval between the two doses. Great care was taken to keep respiratory conditions constant between the baseline and the vasodilator test.

STATISTICAL ANALYSIS AND CALCULATIONS

Values are expressed as means (SD). Statistical analyses were performed with BMDP statistical software. Analysis of variance (ANOVA) for repeated measures was used to test differences between baseline measurements and those after administration of vasodilating agents and

Figure 1 Vasodilator effect on mean pulmonary artery pressure (PAPm). NO, nitric oxide; PGI₂ 10, prostacyclin 10 ng/kg/min; PGI₂ 20, 20 ng/kg/min; FiO₂, fractional inspired oxygen; O₂, oxygen.

between different doses of these drugs. Stability of the baseline values was also tested. A two dimensional ANOVA was used to detect differences between lower and higher levels of inhaled oxygen. Confidence intervals (95% CI) were calculated for main outcome measurements. Regression analysis was used to examine the association between variables. A p value of less than 0.05 was significant.

Results

BASELINE MEASUREMENTS

Ventilation stability during the study was determined by arterial pH and the partial pres-

sure of carbon dioxide. At the start of the study the mean (SD) pH was 7.38 (0.05) and pCO₂ 40.5 (5.8) mm Hg. There was no statistical or clinical evidence of conspicuous pH variation. Three patients who were not intubated had a greater tendency to hypercapnia. Analysis of the pCO₂ values using ANOVA, dividing according to the inspired oxygen fraction, however, showed that this variation was not significant ($p = 0.07$).

Oxygen consumption was measured at the start of catheterisation to achieve reliable vascular resistance values (mean value 146.7 ml/min/m²). There was remarkable variance between individuals (range 94.4–218.0 ml/min/m²), and oxygen consumption was dependent on age ($r = -0.63$, $p = 0.03$) and correlated with heart rate ($r = 0.66$, $p = 0.015$). Haemodynamic baseline values were measured and calculated immediately before vasodilator exposure. Baseline stability was tested after dividing the analyses according to oxygen concentration. Instability in the baseline ratio of mean pulmonary to systemic artery pressure occurred only when fractional inspired oxygen (FiO₂) was > 0.9 .

VASODILATOR EFFECTS ON PULMONARY ARTERY PRESSURE

Responses for NO and prostacyclin were independent of basic oxygen concentration. NO and prostacyclin significantly reduced PAPm; NO reduced PAPm by 5.50 mm Hg (95% CI -7.98 to -3.02) ($p = 0.001$) at the lower oxygen concentration (FiO₂ 0.3). The decrease was maximal at 40 ppm; 80 ppm had no additional effect. Pure oxygen did not alter PAPm. There was a dose-response between the NO doses of 20 and 40 ppm at both oxygen concentrations ($p = 0.02$, ANOVA) and between the prostacyclin doses of 10 and 20 ng/kg/min ($p = 0.04$) (fig 1). The individual response at 20 and 40 ppm NO varied. Figure 2 shows the changes from the preceding baseline values.

Figure 2 Change (%) in mean pulmonary arterial pressure (PAPm) from the preceding baseline value at nitric oxide (NO) concentrations of 20 and 40 ppm in all patients ($n = 20$), including non-responders, when the fractional inspired oxygen is (A) 0.3 or (B) > 0.9 .

Figure 3 Effect of nitric oxide (NO) on the pulmonary vascular resistance index in patients with pulmonary hypertension and either with ($n = 16$) or without ($n = 4$) left to right shunt.

VASODILATOR EFFECTS ON PULMONARY RESISTANCE

Pure oxygen effectively decreased pulmonary vascular resistance: the PVRI declined by 3.18 Um^2 (95% CI -4.80 to -1.56 , $p = 0.0006$). There was a negative linear correlation between the effect of oxygen and the basic PVRI ($r = -0.78$, $p = 0.0003$) in patients with congenital heart disease ($n = 16$). The response to inhaled NO at low oxygen concentration was maximal with even the smallest concentration (20 ppm): the PVRI decreased from 9.1 to 7.7 Um^2 (mean change -1.37 ; 95% CI -2.37 to -0.41 , $p = 0.007$). No dose response was seen, and 80 ppm NO had a smaller effect on the PVRI than 20 or 40 ppm. Patients with pulmonary hypertension related to other causes than congenital heart defect had initially higher pulmonary vascular resistance, but they still had significant vasodilation (fig 3).

Prostacyclin infusion caused the PVRI to decrease more than with the high fraction of inspired oxygen alone and there was a dose-response ($p = 0.039$): maximum vasodilatation was reached with a dose of 20 ng/kg/min , as the PVRI decreased from the preceding value by 1.06 Um^2 (95% CI -1.95 to -0.17).

SYSTEMIC EFFECTS

The systemic vascular resistance index (SVRI) and systemic vascular pressure were not changed by either adding NO or increasing the oxygen fraction. Prostacyclin had a strong effect on the SVRI, which decreased by 6.8 Um^2 (95% CI -10.20 to -3.43) with the maximal dose ($p < 0.0001$). The impact of prostacyclin on the SVRI was dose dependent ($p = 0.006$). The ratio of mean pulmonary to mean systemic artery pressure, however, tended to rise during prostacyclin infusion (fig 4). Most patients had clinical symptoms of systemic hypotension. In many patients prostacyclin also increased the ratio of pulmonary to systemic vascular resistance from the preceding baseline; this change was significant from that of other vasodilators in this study ($p = 0.0002$).

Figure 4 Ratio of mean pulmonary artery pressure (PAPm)/mean systemic artery pressure (SAPm) at a nitric oxide (NO) concentration of 40 ppm and a prostacyclin (PGI_2) dose of 20 ng/kg/min when the fractional inspired oxygen (FiO_2) value is > 0.9 .

The high FiO_2 lowered the ratio of pulmonary to systemic vascular resistance from 0.45 to 0.31 (95% CI for the change -0.23 to -0.05 , $p = 0.0006$). Maximal decrease in the ratio of pulmonary to systemic vascular resistance was achieved with a combination of NO 80 ppm and oxygen (-0.18 , 95% CI -0.26 to -0.10).

CHANGES IN PULMONARY BLOOD FLOW

The change in inhaled oxygen concentration from 30% to 100% led to a significant increase in pulmonary blood flow in 16 patients with left to right shunt (mean change 8.52 ; 95% CI -0.15 to 17.20 l/min/m^2 , $p = 0.005$). Neither NO nor prostacyclin increased the effect of high FiO_2 on pulmonary blood flow index.

REVERSED ORDER

Pure oxygen was tested before NO delivery in five additional patients with secondary pulmonary hypertension to examine whether NO sensitises arterial muscle cells to oxygen. There was no evidence of a carry over effect (data not shown).

METHAEMOGLOBINAEMIA

At the start of the study the mean (SD) metHb concentration was $0.7(0.48)\%$. Maximal NO inhalation (80 ppm) caused a mean (SD) rise to $2.7(1.4)\%$. In the next five minutes the metHb concentration continued to increase to $2.9(1.6)\%$. The high FiO_2 combined with NO significantly raised the metHb concentration: a peak value of 3.3% (mean difference 0.61 ; 95% CI 0.33 to 0.89% , $p < 0.0001$) was reached after inhalation of pure oxygen and NO at 80 ppm for five minutes. Linear regression analysis showed a negative association between this maximal metHb concentration and the logarithm for age ($r = -0.62$, $p = 0.005$).

Discussion

NO, the endothelium derived relaxing factor, participates in maintaining normal vascular tone in systemic and pulmonary vessels. Endothelium dependent pulmonary artery relaxation is impaired in patients with primary and secondary pulmonary hypertension and after cardiopulmonary bypass.^{19 20} As an inhaled gas NO, a magic bullet, has rapidly become an important option in the treatment of life threatening postoperative pulmonary hypertensive crisis. In patients with congenital heart disease, however, there are only a few clinical trials on the dose response of NO or comparisons with other vasodilatory drugs.²¹⁻²⁵

In this study NO was used to assess pulmonary vasoreactivity in patients with either congenital heart disease or evidence of pulmonary vascular disease, or both. Inhaled NO selectively dilated the pulmonary vascular bed without systemic side effects. The dose response of NO at 20, 40 and 80 ppm was examined; in previous trials concentrations up to 80 ppm have been safe and effective.^{5 13 22} Maximal response was achieved at 40 ppm. The effect was potentiated with subsequent oxygen. Prostacyclin acted as a potent vasodilator, affecting the systemic and pulmonary vascular beds.

Prostacyclin was tested only with a FiO_2 value of more than 0.9. Prostacyclin at 20 ng/kg/min was as effective as NO at 40 or 80 ppm with oxygen in lowering pulmonary vascular resistance or pressure, but many patients had systemic effects.

DOSE-RESPONSE

The effect of 20 and 40 ppm NO on PAPm showed a dose response, the difference being significant. Pulmonary vascular resistance was changed less by 80 ppm NO than by 40 ppm. Maximum vasodilatation with hyperoxia was achieved with 80 ppm NO, but the difference between the response to 40 or 80 ppm was not significant. Our results differ from those of Roberts *et al.*,²² who found that maximum reduction in the PVRI at a FiO_2 of 0.21–0.3 was achieved with 80 ppm NO.

Many of our patients had moderately raised pulmonary vascular resistance (table 1). What grade of reactivity is sufficient to guarantee the safety of operating on a patient with congenital cardiac disease and secondary pulmonary hypertension? Linear correlation between basic pulmonary vascular resistance and the vasodilatory effect of oxygen was seen in patients with left to right shunting and secondary changes in pulmonary circulation. One patient with primary pulmonary hypertension and both pulmonary pressure and resistance higher than corresponding systemic values was able to react with considerable vasodilatation (patient number 19, table 1). Vasodilatation is usually absent or weak when there is a very high ratio of pulmonary to systemic vascular resistance. The decrease in pulmonary vascular resistance or pressure in patients with intracardiac shunts did not differ from that in those with pulmonary hypertension due to other aetiology.

SIDE EFFECTS OF NITRIC OXIDE

metHb and formation of NO_2 are side effects of treatment with NO.²⁶⁻²⁹ An association between age and increased metHb concentrations was found. Hyperoxia combined with 80 ppm NO clearly raised the metHb percentage, but the short exposure time limited metHb formation. The rise in metHb concentration was about 2.0(1.2)%. Exposure to latent free radicals formed by NO through its unpaired electron is a potential danger. NO concentrations greater than 80 ppm cause a rapid increase in NO_2 formation^{28 29} and nitrous and nitric acids are consequently formed. In our study, however, NO_2 was kept within the reported safety limit of 5%. A high oxygen concentration accelerated NO_2 formation in our patients, as was also found by Foubert *et al.*²⁹

CLINICAL IMPLICATIONS

NO as a gaseous vasodilator is easy to administer. Selectivity of the pulmonary circulation allows inhaled NO at low concentrations to be considered as a safe and reliable vasodilator in patients with congenital heart disease. NO inhalation was not administered in patients with heart defects associated with mitral or aortic stenosis. Pulmonary oedema is a possible consequence in those with obstructions in the left heart. Inhaled NO might be useful in evaluating the vasodilating capacity of patients with primary hypertension. Lack of reactivity may indicate a poor prognosis and the need for early lung or heart lung transplantation. One of the advantages of NO in cardiac catheterisation is its short half life. The haemodynamic effects of NO on the pulmonary circulation are more obvious than those of prostacyclin, which may dilate systemic arteries even more than pulmonary vessels. Unlike oxygen, inhaled NO, in addition to increasing pulmonary flow, is able to reduce pulmonary arterial pressure. Maximal decrease in pulmonary vascular pressure was achieved with an inhaled NO concentration of 40 ppm.

Recommendations for preoperative vasodilator testing are: to assess the effect of pharmaceutical treatment on pulmonary artery pressure 40 ppm should be delivered for five minutes followed by pure oxygen for 10 minutes; and to quantify maximum vasodilatation 40 ppm NO should be added to the high oxygen concentration for five minutes. Preoperative testing with NO in patients with intracardiac shunts and secondary pulmonary hypertension may prove useful in evaluating operability. Moreover, patients with clearly raised but reactive pulmonary vascular resistance should be given the possibility of NO treatment immediately after bypass in the operating theatre.

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