Effect of inhaled nitric oxide on raised pulmonary vascular resistance in children with congenital heart disease

P Winberg, B P W Lundell, L E Gustafsson

Abstract

Objective—To study the short-term effects of inhaled nitric oxide in infants and young children with congenital heart disease.

Setting—A supraregional referral centre for children with congenital heart disease.

Patients and methods—22 infants and children aged 3–32 months (median age 5 months) with congenital heart disease undergoing preoperative cardiac catheterisation. All but one infant had intra-cardiac shunt lesions and 13 had increased pulmonary vascular resistance. During catheterisation the patients inhaled nitric oxide in a concentration of 40 parts per million in room air. Pulmonary and systemic haemodynamic variables were evaluated by means of measured oxygen consumption and the Fick principle before and after 10 minutes' exposure to nitric oxide.

Results—Inhaled nitric oxide did not affect the systemic circulation. There was a significant reduction in the pulmonary vascular resistance, but only in the 13 infants with pulmonary hypertension, in whom pulmonary vascular resistance was reduced by 34% from 8.6 (4.6) mm Hg.min.m².l⁻¹ (mean (SD)) to 5.7 (3.5) mm Hg.min.m².l⁻¹. The pulmonary circulation in infants with normal pulmonary vascular resistance was not affected. No statistically significant increase in methaemoglobin was seen, though there were large individual differences. No other side effects were seen.

Conclusion—The present study shows that in infants with congenital heart disease inhaled nitric oxide reduced pathologically increased pulmonary vascular resistance without affecting systemic circulation and without important side effects with brief exposure.

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Increased pulmonary vascular resistance with pulmonary hypertension is a frequent complication in congenital heart disease,¹ and post-operative pulmonary hypertensive crisis is a major problem that may account for a substantial part of the postoperative mortality and morbidity.² Until the discovery of the biological effects of nitric oxide (NO) there was no selective treatment to produce pulmonary vasodilatation. NO is a major endothelium

derived relaxing factor^{3–5} that regulates blood flow and modulates the hypoxic pressor response in the lung.⁶ It is also present in exhaled air of human.⁷ Because it is rapidly inactivated by haemoglobin,⁸ the dilating effects of inhaled NO should be confined to the pulmonary vascular bed. The selective pulmonary vasodilating effect of inhaled NO in hypoxic pulmonary hypertension was shown in lambs⁹ and in healthy volunteers.¹⁰ Inhaled NO was of benefit in the treatment of persistent pulmonary hypertension of the newborn^{11,12} and in the adult respiratory distress syndrome.¹³ Recently Roberts *et al* showed that pulmonary vascular resistance was reduced by NO during cardiac catheterisation in infants with congenital heart disease¹⁴ and we have also reported a dramatic effect in one case of postoperative pulmonary hypertension.¹⁵

NO, however, can cause methaemoglobinemia,¹⁶ and in the presence of oxygen NO forms nitrogen dioxide, which is toxic in the lungs even in very low concentrations.^{17–19} No severe side effects were seen during or after the administration of NO at concentrations below 80 ppm in adults^{10,13} but experience is still limited. In infants and children there is even less experience and the aim of this study was to investigate further the effects and side effects of brief inhalation of NO in infants and children with congenital heart defects.

Patients and methods

We studied 22 infants and children aged 3–32 months (median age 5 months) with congenital heart disease who had routine pre-operative cardiac catheterisation (table). All but one had shunt lesions, and 10 had atrio-ventricular septal defects. Twelve also had Down's syndrome. Pethidine (2 mg/kg), promethazine (0.5 mg/kg), and chlorpromazine (0.5 mg/kg) were used for sedation. One hour before catheterisation a topical anaesthetic containing prilocaine and lignocaine was applied under plastic occlusion to both groins. The maximum area of skin exposed was 15 cm² and the estimated maximum amount of prilocaine and of lignocaine was 60 mg of each.

Right heart catheterisation was performed from a femoral approach and the catheter was advanced to the pulmonary artery. Haemodynamic calculations based on the Fick principle were made from measurements of oxygen uptake and arteriovenous differences in oxygen content over the systemic and

Department of Paediatrics, St Göran's Children's Hospital, Karolinska Institute, Stockholm, Sweden

P Winberg
B P W Lundell

Department of Physiology and Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden
L E Gustafsson

Correspondence to:
Dr P Winberg, St Göran's Children's Hospital, PO Box 12500, S-11281, Sweden.

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Clinical data on 20 patients with congenital heart disease

Patient	Age	Sex	Diagnosis	PH
1	13	F	AVSD, Down	+
2	10	M	VSD	—
3	8	F	AVSD, Down	+
4	7	M	VSD	—
5	5	F	AVSD, Down	+
6	10	F	VSD, ASD	—
7	3	M	AVSD, PDA, Down	+
8	4	F	AVSD, Down	+
9	4	M	AVSD, Down	+
10	4	M	AVSD, Down	—
11	3	M	AVSD	—
12	32	F	op CoA, VSD	+
13	4	M	AVSD, Down	+
14	5	F	VSD, Down	+
15	8	M	AS, MI	+
16	7	F	VSD, Down	—
17	4	F	AVSD, Down	+
18	5	M	VSD, PDA, Down	+
19	26	F	DORV, MS	+
20	19	F	PAPVR	—

PH, pulmonary hypertension; AVSD, atrioventricular septal defect; VSD, ventricular septal defect; ASD, atrial septal defect; PDA, persistent ductus arteriosus; DORV, double outlet right ventricle; CoA, coarctation of the aorta; MI, mitral insufficiency; AS, aortic stenosis; MS, mitral stenosis; PAPVR, partial anomalous pulmonary venous return.

pulmonary vascular beds. To measure oxygen uptake we placed a transparent Plexiglass hood (volume 17 l) over the head of the infant and sealed it around the neck with thin plastic wrap. Room air was continuously drawn through the system at a known rate by a vacuum pump and a Pneumotach (4000 VR, Vertek Series, Hewlett-Packard, Palo Alto, CA, USA). The hood effluent was collected for 1 min and the oxygen concentration was determined to within 0.01 volume per cent by a paramagnetic oxygen analyser (Magnos 2T, Hartmann and Braun AG, Frankfurt am Main, Germany). Intravascular pressures were measured with a fluid filled transducer (Hewlett-Packard 1290c, Palo Alto, CA, USA). In patients in whom arterial catheterisation was not performed, systemic pressure was determined by an oscillometric technique²⁰ in the right upper arm to obtain simultaneous pressure recordings of the systemic and pulmonary circulations.

After oxygen uptake was measured, the hood was used to administer NO (fig 1). We ensured a high turnover of the gas volume in

the hood; to avoid accumulation of NO₂, by setting the vacuum pump at a rate of 40 l.min⁻¹ NO from a stock concentration of 1000 parts per million (ppm), kept in pure nitrogen in a cylinder (AGA-Gas AB, Lidingö, Sweden) was added to the system by a flow meter at a rate calculated to give a f_iNO of 40 ppm. The addition of NO/N₂ reduced f_iO₂ to approximately 0.20. The NO and NO₂ concentrations in the hood were monitored by a chemiluminescence technique (Monitor Labs 8840, Lear Siegler Measurements Controls, Englewood, CO, USA).²¹ After 10 minutes' exposure to NO a new set of pressure recordings and oxygen content measurements was obtained. Vascular resistance was calculated in indexed Wood units, Um² = mm Hg.min.m².l⁻¹, and a pulmonary vascular resistance above 4 Um² was regarded as abnormal. Blood samples for methaemoglobin analysis (ABL 520, Radiometer, Copenhagen, Denmark) were drawn before and at the end of the NO exposure.

The study was approved by the Swedish Medical Products Agency and the local ethics committee. Informed parental consent was obtained before catheterisation. We used a paired *t* test and linear regression for statistical analysis.

Results

Because one infant periodically did not maintain free airways hypoventilation and considerable variations in systemic oxygen

Figure 1 System for administration and monitoring of NO during cardiac catheterisation.

Figure 2 Pulmonary vascular resistance in 20 infants and children with congenital heart disease before and during inhalation of 40 ppm NO. PVR, pulmonary vascular resistance. Um², mm Hg.min.m².l⁻¹.

Figure 3 Initial pulmonary vascular resistance and effect of inhalation of 40 ppm NO on pulmonary resistance in 13 infants and children with congenital heart disease and increased pulmonary vascular resistance. PVR, pulmonary vascular resistance. dPVR, change in PVR. Um^2 , $\text{mm Hg} \cdot \text{min} \cdot \text{m}^2 \cdot \text{L}^{-1}$.

saturation ensued. In one infant with a considerable flow in the ductus the catheter could not be advanced into a pulmonary branch. This made calculations of pulmonary flow index and resistance unreliable and these infants were excluded. Otherwise the patients were stable during catheterisation and the NO exposure and showed only small variations in systemic saturation. Mean (SD) arterial PCO_2 was slightly increased ($5.8 (0.64)$ kPa) but did not exceed 6.8 kPa. There was a slight but significant increase in heart rate from $133 (16)$ beats/min to $139 (19)$ beats/min ($p < 0.001$) during NO exposure. Figure 2 shows the effect of NO on the pulmonary vascular resistance. In the seven patients with a normal pulmonary vascular resistance no significant effects were seen, whereas in all patients with raised pulmonary vascular resistance ($n = 13$) a reduction in resistance was seen. The mean reduction was 34%, from $8.6 (4.6)$ Um^2 to $5.7 (3.5)$ Um^2 ($p < 0.001$), and there was a linear relation between baseline pulmonary vascular resistance and the reduction (fig 3).

Figure 4 Mean pulmonary artery pressure and pulmonary blood flow (pulmonary index) before and during inhalation of 40 ppm NO in 13 infants and children with congenital heart disease and increased pulmonary vascular resistance. mPAP, mean pulmonary artery pressure.

Figure 5 Methaemoglobin concentration before and during inhalation of 40 ppm NO in 22 infants and children with congenital heart disease. Met Hb%, methaemoglobin fraction of total haemoglobin.

The effect on pulmonary artery pressure became obvious within a few minutes. In seven patients studied 10 min after discontinuation of NO, pulmonary vascular resistance had again increased but not to the pre-exposure value. All patients but one had intracardiac shunt lesions and consequently the direct effect of pulmonary vasodilatation on pulmonary artery pressure was lessened by an increased intracardiac shunt and increased pulmonary flow (fig 4). Pulmonary flow increased from $6.2 (2.2)$ $\text{l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ to $8.1 (4.7)$ $\text{l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ($p < 0.05$), and the mean pulmonary artery pressure decreased from $48.9 (12.9)$ mm Hg to $38.4 (12.3)$ mm Hg ($p < 0.001$). No change in systemic artery pressure was seen. Four infants had raised methaemoglobin concentrations ($> 2\%$ of total haemoglobin) before NO exposure, possibly owing to the topical application of prilocaine. For the whole group there was no significant increase in methaemoglobin. However, large individual differences were seen (fig 5). No bleeding problems or any other side effects were seen during or after catheterisation.

Discussion

This study shows that inhalation of NO selectively dilated the pulmonary vascular bed in infants with congenital heart disease and with raised pulmonary vascular resistance. Preoperative cardiac catheterisation offers a good opportunity to study the basic effects and side

effects of inhaled NO. A thorough invasive evaluation of the haemodynamic consequences of NO inhalation may be carried out under controlled conditions. The premedication might cause some hypoventilation and thus affect the circulation: this, however, was a significant problem in only one infant.

NO is a potentially toxic gas and the experience of NO inhalation in children is limited. To reduce the risk of accidental intoxication we used a stock gas with a NO concentration of 1000 ppm (0.1%) certified to contain less than 15 ppm NO₂, and both NO and NO₂ concentrations in the hood were monitored. The time weighted average for 8 h daily human exposure to NO and NO₂ by the US occupational Safety and Health Administration is set at 25 ppm and 5 ppm respectively.²² The corresponding Swedish limit for NO₂ is 2 ppm. Measurements before patient exposure indicated that at 40 ppm NO, the NO₂ concentration was below 2 ppm, whereas significantly higher values were reached at 80 ppm. Thus patient exposure was limited to 40 ppm NO. Cigarette smoke contains 400–1000 ppm NO.²³ Consequently, we did not consider that this brief exposure constituted a significant risk.

Determinations of flow index and resistance in the pulmonary and the systemic circulation in infants with shunt lesions are complex and the indicator dilution techniques are unreliable. A technique based on measured oxygen consumption and the Fick principle is currently regarded as the most reliable method. However, each calculation requires a new set of blood samples from pulmonary and systemic arteries and veins to determine the oxygen content. This is time consuming and precludes numerous determinations of flow and resistance. Since most infants evaluated for cardiac surgery are small, and some may be in heart failure, the procedure must not be unduly prolonged. Therefore NO was given in only one concentration and the dose-response effect could not be investigated. In lambs up to 80 ppm NO is required to reverse fully hypoxic vasoconstriction,⁹ whereas in human adults as little as 10 ppm NO can completely dilate the pulmonary vascular bed.¹⁰ The concentration of 40 ppm was chosen because it was expected to give sufficient vasodilatory effect, to be well below toxic NO concentrations, and to minimise NO₂ exposure. In a recently published report, also on the effect of inhaled NO in infants during catheterisation, Roberts *et al* used 20, 40, and 80 ppm NO sequentially.¹⁴ They found the greatest reduction in pulmonary vascular resistance with 80 ppm NO, but the effect was not significantly different from that of 40 ppm and the different concentrations were only tried in an ascending sequence, which makes it difficult to evaluate the dose-response curve. In that study the mean reduction in pulmonary vascular resistance was 26%, with inhalation of 80 ppm NO, compared with 34% in our study.

Changes in pulmonary vascular resistance may be difficult to detect when baseline pulmonary vascular resistance is low. None the

less our findings of no response to NO when resistance is normal accord with earlier studies in both lambs and humans.^{9,10} The dependence of the pulmonary vascular response to NO on initial pulmonary vascular resistance suggests that the NO vasodilator tone may be disturbed in pulmonary hypertension associated with congenital heart disease. This accords with other findings indicating that endothelial dysfunction is an early event in the development of pulmonary vascular disease in infants with congenital heart disease.^{24,25} In the infants with raised pulmonary vascular resistance, NO reduced but did not normalise pulmonary vascular resistance, and there was a linear relation between initial pulmonary vascular resistance and the reduction by NO (fig 3). This indicates that only a part of the increased pulmonary vascular resistance is susceptible to influence by NO. The remaining increase in pulmonary vascular resistance during NO breathing may be attributed to structural changes in the pulmonary vessels¹ or perhaps to secondary vasoconstriction not affected by NO. NO inhalation is known to abolish hypoxic pulmonary vasoconstriction,^{9,10} and several of the infants we studied did not have full systemic oxygen saturation. However, there was no relation between initial left atrial or aortic oxygen saturation and the reduction in pulmonary vascular resistance induced by NO, indicating that the effect of inhaled NO in these infants reflects more than a reversal of hypoxic vasoconstriction.

Ten of the 13 infants with increased pulmonary vascular resistance, had Down's syndrome: this distribution is typical of patients with pulmonary hypertensive problems.²⁶ Chronic hypoventilation and underdevelopment of the pulmonary vascular bed are two reported causes of the high incidence of pulmonary hypertension in patients with Down's syndrome.^{27,28} Furthermore, many infants with Down's syndrome have atrioventricular septal defects and this malformation is frequently associated with increased pulmonary vascular resistance irrespective of chromosomal abnormalities.²⁹ The three infants without Down's syndrome showed an average reduction in pulmonary vascular resistance of 32%, and the four infants with a heart malformation other than an atrioventricular septal defect showed a mean reduction of 38%. This indicates that the response to NO is related primarily to vascular resistance itself rather than to the underlying cardiac malformation or chromosome aberration.

Though this brief exposure had no statistically significant effect on methaemoglobin, there were large individual differences. A few infants reached concentrations at which methaemoglobin could have a negative effect (fig 5). This indicates that methaemoglobin must be monitored closely if NO is used for longer periods. NO also affects platelet activity⁵ but no bleeding problems were seen during or after catheterisation.

In conclusion, we found that brief inhalation of NO reduced the increase in pulmonary

vascular resistance in children with congenital heart disease without affecting systemic circulation and without causing important side effects. The findings suggest that the NO vasodilator tone in the lungs is disturbed in infants with congenital heart disease and increased pulmonary vascular resistance. Inhaled NO is the first substance that has been shown to cause a selective dilatation in the pulmonary vascular bed in infants with congenital heart disease and pulmonary hypertension. The results encourage us to consider the possibility of using inhaled NO to treat postoperative pulmonary hypertensive crises and studies are currently under way.

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- Hoffman JIE, Rudolph AM, Heyman MA. Pulmonary vascular disease with congenital heart lesions: Pathologic features and causes. *Circulation*. 1981;64:873-7.
- Hopkins RA, Bull C, Haworth SG, de Laval MR, Stark J. Pulmonary hypertensive crises following surgery for congenital heart defects in young children. *Eur J Cardiothorac Surg* 1991;5:628-34.
- Palmer RMJ, Ferrige AG, Moncada S. Nitric oxide release accounts for the biological activity of endothelium derived relaxing factor. *Nature* 1987;327:524-6.
- Ignarro LJ, Buga GM, Wood KS, Byrnes RE, Chaudhuri G. Endothelium-derived relaxing factor produced and released from artery and vein is nitric oxide. *Proc Natl Acad Sci USA* 1987;84:9265-9.
- Moncada S, Palmer RMJ, Higg EA. Nitric oxide: Pathophysiology, and pharmacology. *Pharmacol Rev* 1991;43:109-42.
- Persson MG, Gustafsson LE, Wiklund NP, Moncada S, Hedqvist P. Endogenous nitric oxide as a probable modulator of pulmonary circulation and hypoxic pressor response in vivo. *Acta Physiol Scand* 1990;140:449-57.
- Gustafsson LE, Leone AM, Persson MG, Wiklund NP, Moncada S. Endogenous nitric oxide is present in the exhaled air of rabbits, guinea pigs and humans. *Biochem Biophys Res Commun* 1991;181:852-7.
- Gibson QH, Roughton FJW. The kinetics and equilibration of reactions of nitric oxide with sheep hemoglobin. *J Physiol* 1957;136:507-26.
- Frostell C, Fratacci MD, Wain JC, Jones R, Zapol WM. Inhaled nitric oxide: A selective pulmonary vasodilator reversing hypoxic pulmonary vasoconstriction. *Circulation* 1991;83:2038-47.
- Frostell CG, Blomqvist H, Hedenstierna G, Lundberg J, Zapol WM. Inhaled nitric oxide selectively reverses human hypoxic pulmonary vasoconstriction without causing systemic vasodilatation. *Anesthesiology* 1993;78:413-6.
- Roberts JD, Polander DM, Lang P, Zapol WM. Inhaled nitric oxide in persistent pulmonary hypertension of the newborn. *Lancet* 1992;340:818-9.
- 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.
- Rossaint R, Falke KJ, Pison U, 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.
- Roberts Jr JD, Lang P, Bigatello LM, Vlahakes GJ, Zapol WM. Inhaled nitric oxide in congenital heart disease. *Circulation* 1993;87:447-53.
- Sellden H, Winberg P, Gustafsson LG, Lundell B, Böök K, Frostell CG. Inhalation of nitric oxide reduced pulmonary hypertension after cardiac surgery in a 3-2 kg infant. *Anesthesiology* 1993;78:577-80.
- Chiodi H, Mohler JG. Effects of exposure of blood hemoglobin to nitric oxide. *Environ Res* 1985;37:355-63.
- Stavert DM, Lehnert BE. Nitric oxide and nitrogen dioxide as inducers of acute pulmonary injury when inhaled at relatively high concentrations for a brief period. *Inhal Toxicol* 1975;2:53-67.
- Hugod C. Effect of exposure to 43 ppm nitric oxide and 3-6 ppm nitrogen dioxide on rabbit lung. *Int Arch Occup Environ Health* 1978;42:159-67.
- Hugod C. Effect of exposure to 43 ppm nitric oxide and 3-6 ppm nitrogen dioxide on rabbit lung. *Int Arch Occup Environ Health* 1978;42:159-67.
- von Nieding G, Wagner HM. Vergleich der Wirkung von Stickstoffdioxid und Stickstoffmonoxid auf die Lungenfunktion des Menschen. *Staub-Reinhardt Luft* 1975;35:175-8.
- Kimble KJ, Darnall R, Ayelderman M, Ariagno RL, Ream AK. An automated oscillometric technique for estimating mean arterial pressure in critically ill newborns. *Anesthesiology* 1981;54:423-5.
- Fontijn A, Sabadell AJ, Ronco RJ. Homogeneous chemiluminescent measurement of nitric oxide with ozone. *Anal Chem* 1970;42:575-9.
- OSHA excursion limits. *MMWR Morb Mortal Wkly Rep* 1988;37:21.
- Norman V, Keith C. Nitrogen oxide in tobacco smoke. *Nature* 1965;205:915-6.
- Rich S, Brundage BH. Pulmonary hypertension: A cellular basis for understanding the pathophysiology and treatment. *J Am Coll Cardiol* 1989;11:545-50.
- Celermajer DS, Cullen S, Deanfield JE. Impairment of endothelium-dependent pulmonary artery relaxation in infants with congenital heart disease and abnormal pulmonary hemodynamics. *Circulation* 1993;87:440-6.
- Chi T, Krovetz J. The pulmonary vascular bed in children with Down syndrome. *Pediatrics* 1975;86:533-8.
- Cooney TP, Thurlbeck WM. Pulmonary hypoplasia in Down syndrome. *N Engl J Med* 1982;307:1170-3.
- Levine RO, Simpser M. Alveolar hypoventilation and cor pulmonale associated with chronic airway obstruction in infants with Down syndrome. *Clin Pediatr* 1982;21:25-9.
- Haworth SG. Pulmonary vascular bed in children with complete atrioventricular defect: Relation between structural and hemodynamic abnormalities. *Am J Cardiol* 1986;57:833-9.