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 intracardiac 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.m.-2.1-4 (mean (SD)) to 5-7 (3-5) mm Hg.min.m.-2.1-4. 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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Patients and methods

We studied 22 infants and children aged 3–32 months (median age 5 months) with congenital heart disease who had routine preoperative cardiac catheterisation (table). All but one had shunt lesions, and 10 had atrioventricular 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
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### Clinical data on 20 patients with congenital heart disease

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<td>20</td>
<td>19</td>
<td>F</td>
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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, Vertex 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 percent 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 technique 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 fNO of 40 ppm. The addition of NO/NO₂ reduced fO₂ 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). 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.m⁻².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.](image1)

![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.](image2)
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. Um², mm Hg.min.m⁻².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 Pco₂ 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) Um² to 5·7 (3-5) Um² (p < 0·001), and there was a linear relation between baseline pulmonary vascular resistance and the reduction (fig 3).

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) l.min⁻¹.m⁻² to 8·1 (4·7) l.min⁻¹.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 hypventilation 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 initial pulmonary vascular resistance of the infants with Down syndrome, and the Swedish norm for healthy infants, suggest that only brief exposure to NO 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.\textsuperscript{6,10} The dependence of the pulmonary vascular response to NO on initial pulmonary vascular resistance suggests that the NO vasodilator effect might be inhibited by NO, which is an early event in the development of pulmonary vascular disease in infants with congenital heart disease.\textsuperscript{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 vessels\textsuperscript{1} or perhaps to secondary vasoconstriction not affected by NO. NO inhalation is known to abolish hypoxic pulmonary vasoconstriction,\textsuperscript{8,10} 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.\textsuperscript{26} Chronic hypventilation and underdevelopment of the pulmonary vascular bed are two reported causes of the high incidence of pulmonary hypertension in patients with Down's syndrome.\textsuperscript{27,28} Furthermore, many infants with Down's syndrome have atriovenous septal defects and this malformation is frequently associated with increased pulmonary vascular resistance irrespective of chromosomal abnormalities.\textsuperscript{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 atriovenous 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 activity\textsuperscript{4} 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 significant 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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