Inhaled Nitric Oxide to Newborns and Infants after Congenital Heart Surgery on Cardiopulmonary Bypass

A Dose-response Study

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Twelve patients (median age 3.8 months) with pulmonary hypertension in the postoperative period after congenital heart surgery on cardiopulmonary bypass were given inhaled nitric oxide. Effects on cardiovascular and respiratory systems were measured. Mean pulmonary artery pressure decreased from 33 ± 2 to 28 ± 2 mmHg ($p < 0.001$) and arterial oxygen tension increased from 13.3 ± 2.3 to 16.7 ± 2.7 kPa ($p < 0.05$). The mean change in arterial oxygen tension in percent was $29.8 \pm 6.3\%$ ($p < 0.05$). The response was significant only in the first step from 0 to 3 or 5 ppm with no further significant changes in mean pulmonary artery pressure or oxygenation at higher doses. The decrease in mean pulmonary artery pressure was concomitant with a significant increase in arterial oxygen tension. No dose-response relationship was found with increasing doses to 80 ppm.

Key words: cardiopulmonary bypass, children, congenital heart defect, inhaled nitric oxide, new-born, pulmonary hypertension.

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Pulmonary hypertension is a well-known phenomenon after correction of congenital heart disease with large left to right shunt (1, 2). At least two factors predispose for pulmonary hypertension (PHT) postoperatively. One is high blood flow through the pulmonary vascular tree because of the congenital heart defect, where the amount and the duration of flow seem to have a major impact on the degree of PHT (3). Secondly, we know that cardiopulmonary bypass itself changes the balance of the endothelium-derived vasoactive factors, resulting in vasoconstriction because of less nitric oxide (NO) release and increased levels of endothelin-1 (4–6).

In 1987–1988, several groups suggested independently that NO was the endothelium-derived relaxing factor (7–9). In 1988, inhaled nitric oxide (iNO) was first shown to be a pulmonary vasodilator in primary pulmonary hypertension and in 1991 it was shown to be a selective pulmonary vasodilator (10–12). Since 1992, iNO has been used in the treatment of persistent pulmonary hypertension of the newborn (PPHN) in several studies (13–16). It has also been shown to reduce the need of ECMO in this disease (17). In several studies, iNO has been used prior to heart surgery, establishing the reversibility of the PHT and thus providing the indication for surgery (18–20). Postoperatively, after congenital heart surgery, iNO has been used in a wide range of doses from 2 to 80 ppm. The optimal dosage has not yet been established (21–27).

The first aim of this study was to evaluate dose-response, starting with a relatively low dose of 3 or 5 ppm, with stepwise increments up to 40 or 80 ppm. Secondly, we wanted to determine whether there is a difference in dosage needed to obtain the effects on oxygenation and the pulmonary artery pressures, as has been discussed by other investigators (19, 20, 27)

MATERIAL AND METHODS

The study was approved by the ethics committee at the University of Göteborg and performed after parental consent.

The study was performed during postoperative care in a pediatric intensive care unit (PICU) after surgical correction of congenital heart disease. Patients were treated with conventional mechanical ventilation, with no changes in ventilatory settings, FiO_2, fluids, inotropic support or vasodilators used during the study unless absolutely necessary. The patients were sedated

with continuous infusions of morphine and midazolam and they were disturbed as little as possible during the study.

According to our protocol, all patients where pulmonary hypertension was anticipated were fitted with pulmonary artery catheters during surgery (18G Epidural Catheter, Portex AB, Sollentuna, Sweden). A thermodilution pulmonary artery catheter (Baxter Medical AB, Kista, Sweden) was placed in some patients for cardiac output measurements in the post-operative period.

The study was initiated when the patients showed signs of pulmonary hypertension, defined as mean pulmonary artery pressure (mPAP) >20 mmHg or mPAP/mean systemic artery pressure (mSAP) >0.25. The study was performed on the day of surgery ($n = 2$), the morning after surgery ($n = 6$) or on the second day after surgery ($n = 4$). After a 30-min baseline period with stable values of ventilation and circulation, NO was introduced in stepwise increments with 5, 10, 20 and 40 ppm (Group I $n = 6$) or 3, 10, 30 and 80 ppm (Group II $n = 6$) and was then returned to zero in both groups. After 10 min on each dose, systemic and pulmonary blood pressures, cardiac output (CO), ventilatory parameters, blood gases and methemoglobin (metHb) were registered. All parameters were also closely followed when returning to 0 ppm. Inhaled NO was reintroduced if a rebound phenomenon with mPAP higher than baseline values was registered.

The NO gas used was Medical Nitric Oxide AGA 1000 ppm (AGA Gas AB, Sundbyberg, Sweden). Nitric oxide was administered using different NO-administration equipment. NOMIUS Classic (Department of Medical Technology, Sahlgrenska University Hospital, Göteborg, Sweden) and DelNO (Intramedic AB, Bålsta, Sweden) were used with SERVO 900 mechanical ventilator (Siemens AB, Solna, Sweden) or Sechrist (Sechrist Ind. Inc., Anaheim, CA, USA). The Nodomo equipment was used with the Dräger Babylog 8000 Infant Ventilator (Dräger AB, Stockholm, Sweden), while in Siemens 300 mechanical ventilator (Siemens AB, Solna, Sweden), the built-in NO-delivery equipment was used. The levels of NO and nitrogen dioxide (NO_2) were measured by means of Notoo (prototype, Department of Medical Technology, Sahlgrenska University Hospital, Göteborg, Sweden) or MicroMedical electrochemical fuel cells (Medela AB, Täby, Sweden) in the inspiratory limb of the ventilatory circuit. Blood pressures were measured with a pressure transducer set (BOC Ohmeda, Helsingborg, Sweden). A CO monitor (Baxter COM 2 P, Baxter Medical AB, Kista, Sweden) was used for these measurements and CO was calculated as a mean of three measurements 1–3 min apart, with injection of 3 ml of 5–10°C saline.

The data are presented on each dose as mean values and standard error of the mean of the change in PaO_2, $PaCO_2$, mPAP, mSAP and CO and tested for significance by paired two-tailed *t*-test with a confidence interval of 0.95 ($p < 0.05$). Groups were compared with a one-way ANOVA test. Statistical analyses were carried out using StatMost 3.5 (Dataxiom Software Inc., Los Angeles, CA, USA) and graphs have been made in Axum 5.0 (MathSoft International, Bogshot, Surrey, UK).

Patients

Twelve patients (6 males and 6 females) with congenital heart disease corrected on cardiopulmonary bypass (CPB) were included in the study; mean age was 3.8 months (range 1 day to 12.6 months) and mean weight 4.8 kg (range 2.3 to 6.9 kg). The diagnoses were AVSD ($n = 5$), VSD ($n = 4$) alone or in combination with PDA, ASD or CoA, ASD + PDA ($n = 1$), TAPVR with outflow stenosis ($n = 1$) and TGA + VSD + ASD ($n = 1$). All patients had pulmonary artery catheters, five of these were thermodilution catheters. Mean pulmonary artery pressure before the start of the study was 34 mmHg (range 21–47). Mean value of mPAP/mSAP was 0.58 (range 0.34–0,84). Mean FiO_2 before the study was 0.64 (range 0.33–1.0) and this was kept constant during the study.

RESULTS

Effects on pulmonary artery pressures

In group I there was a decrease in mPAP, from 32 ± 3 to 28 ± 3 mmHg ($p < 0.01$), when starting NO with 5 ppm, and an increase in mPAP from 27 ± 3 to 33 ± 4 mmHg ($p < 0.01$), when returning from 40 ppm to zero ppm NO. Group II showed a decrease in mPAP from 36 ± 2 to 28 ± 3 mmHg ($p < 0.05$) in the first step to 3 ppm NO, but the increase in mPAP when returning from 80 ppm NO to zero did not reach statistical significance. Comparing the two groups, grouping the steps 3 and 5 ppm, 20 and 30 ppm and 40 and 80 ppm together, there were no significant differences between the groups with a one-way ANOVA test at each step. Graphs and statistics for each group and for the two groups grouped together are presented in Fig. 1.

Effects on oxygenation

PaO_2 increased in all patients (there were no differences between groups with the one-way ANOVA test, as above) from 13.3 ± 2.3 to 16.7 ± 2.7 kPa ($p < 0.05$). The increase was significant only in the first dose step. There were no further significant changes in PaO_2 with increasing doses of NO (Fig. 2). The overall mean

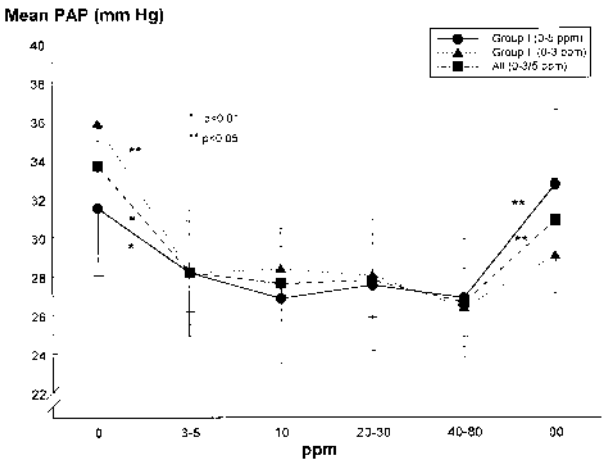

Fig. 1. Mean pulmonary artery pressure (mPAP) in mmHg in response to inhaled nitric oxide (iNO). MPAP decreased in both groups and when grouped together in the first dose step only. Error bars express standard error of the mean.

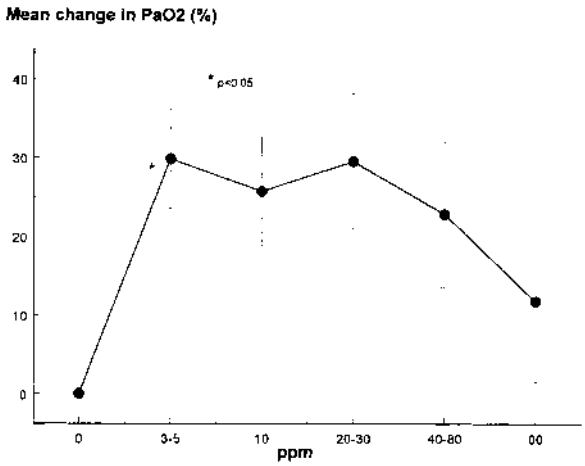

Fig. 3. Mean change in PaO_2 (%) in response to iNO in all patients. PaO_2 increased significantly only in the first dose step. Error bars express standard error of the mean.

percentage increase in PaO_2 with the basal value as zero in the total material was 29.8 ± 6.3 ($p < 0.05$) (Fig. 3).

Effects on $PaCO_2$ and mSAP

There were no significant changes in $PaCO_2$ in Groups I and II and no significant changes in mSAP in Groups I and II or when grouped together as above.

Effects on CO

Only five thermodilution catheters were placed in patients who actually had pulmonary hypertension postoperatively. One catheter failed to give more than baseline values for cardiac output. In the 4 patients where CO was measured, there were no significant changes throughout the study.

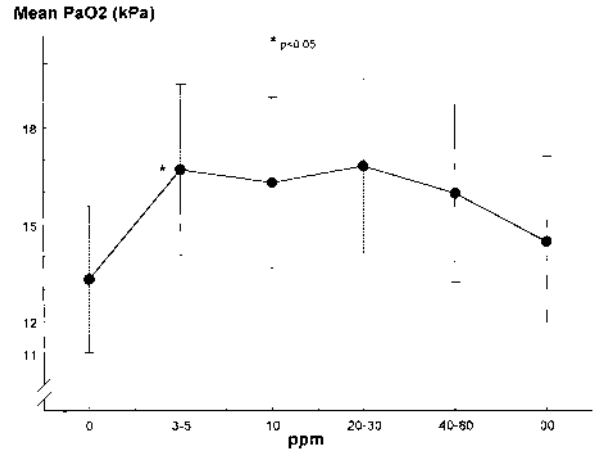

Fig. 2. Mean PaO_2 in kPa in response to iNO in all patients. PaO_2 increased significantly only in the first step from 0 to 3 or 5 ppm NO. Error bars express standard error of the mean.

Measured metHb, NO and NO_2

All patients changed their metHb values (%) with a median of 0.9 (range 0.2–1.5) resulting in maximum metHb values ranging from 1.1 to 2.3. The median change in the patients inhaling 40 ppm NO was 0.6 (range 0.2–0.8) and the median change when inhaling 80 ppm NO was 1.1 (range 0.4–1.5). Four patients were under 3 months of age and had a median change in metHb of 0.9% (range 0.2–1.5).

Measured NO corresponded well to the set dose of ppm. NO_2 rose above 1 ppm in 2 patients to 1.3 ppm at 40 ppm when mixed in 60% O_2 and to 1.7 ppm at 80 ppm when mixed in 100% O_2.

Eight patients had prolonged treatment with iNO. They either increased their oxygen tension >20% when treatment was started or increased their mPAP >20% when the treatment was stopped. The median time of prolonged treatment was 105 h (range 37–195 h). Weaning was uneventful in all patients and was performed when FiO_2 was <0.6 or when the oxygenation index (OI = mean airway pressure * FiO_2/PaO_2 (mmHg)* 100) was below 10.

Mortality in the study group was 1/12. This patient died after three weeks and after a second surgical procedure, where the mitral valve was replaced owing to mitral insufficiency after AVSD correction.

All dose-response studies in the individual patients were performed without technical or medical complications.

DISCUSSION

During the past few years, the positive effect of iNO on pulmonary hypertension and oxygenation in infants after surgery on cardiopulmonary bypass (CPB) has been pointed out in several studies (21–27). This study shows that there is a significant decrease in pulmonary artery pressure at doses of 3 and 5 ppm. This is in contradiction to other findings, where it has been suggested that a higher dose of iNO is needed to change pulmonary artery pressures (19, 27, 28). This change in pulmonary artery pressure seems to reflect a change in pulmonary capillary blood flow, which improves V/Q and substantially improves oxygenation. In contrast to many previous findings but in agreement with Miller et al., we did not find a dose-response relationship in improvement of oxygenation between the initial and maximal dose of NO, that is between 5 and 40 ppm or 3 and 80 ppm. Although oxygenation improved significantly as a result of increased capillary flow and better V/Q, we did not see any significant change in $PaCO_2$. There was a tendency toward a lower $PaCO_2$ value, but this did not reach statistical significance. Major changes in normal levels of $PaCO_2$ could not be expected with this change in pulmonary blood flow.

It is important to determine the lowest possible dose in treatment with iNO, as NO itself could be toxic to the lung tissue. We also know that NO together with oxygen forms NO_2, which could further increase toxicity to the lungs (29). This risk implies that it is necessary to titrate the NO dose for each individual patient and to use the lowest effective dose. However, in our study we have shown that with the doses we have used, up to a maximum of 80 ppm, the levels of NO_2 did not on any occasion reach levels where toxicity could be expected. Furthermore, when iNO was used for prolonged periods of up to 8 days, no toxic levels of NO or NO_2 could be shown as a result of altered metabolism over time (30, 31). Still, it must be pointed out that toxicity of both NO and NO_2 has not yet been fully investigated and clarified.

Another matter of toxicity that has been discussed is whether metHb is formed in toxic amounts during the use of iNO. Especially in newborns, the capacity of methemoglobin reductase might be exceeded as the amount of this enzyme is reduced (32). However, with low-dose exposure to iNO in term infants, metHb values were not elevated in earlier studies (13, 19, 33). In our study we followed the metHb value carefully and this did not reach a level where it could have a negative impact on oxygenation. With low doses of iNO, there seems to be very little risk of exceeding 5% of metHb, which is the level at which oxygen binding capacity might be endangered.

In those patients where iNO was continued after the dose-response study, weaning from iNO was always completed before they were weaned from the ventilator. When the patients were stable without iNO, weaning from the ventilator began. It seems reasonable to safely wean the infants off iNO before weaning them off the ventilator, in order to reduce the risk of withdrawal phenomena. We have had a stable haemodynamic situation in our patients with this regimen and a fairly short stay in the PICU after CPB surgery. In 1997, the median stay in intensive care for VSD and AVSD patients, which reflects the majority of the patients, was 2.0 and 3.5 days, respectively. The total mortality after open-heart surgery including surgery for hypoplastic left heart syndrome was 1.5%, which is very positive.

CONCLUSIONS

We conclude that 3 or 5 ppm inhaled nitric oxide decreases pulmonary artery pressure and improves oxygenation significantly and concomitantly in newborns and infants after open-heart surgery on cardiopulmonary bypass. There was no dose-response relationship between 3 and 80 ppm. Whether there is a dose-response relationship below 3 ppm remains to be investigated. Infants with pulmonary hypertension after open-heart surgery, where iNO was continued after the dose-response study, had a safe, short and stable stay in the PICU. Whether inhaled nitric oxide can be shown to have a significant impact on mortality and/or morbidity in patients with or at risk of developing pulmonary hypertension postoperatively remains to be shown in prospective, randomized controlled studies.

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