Residual pulmonary hypertension in children after treatment with inhaled nitric oxide: a follow-up study regarding cardiopulmonary and neurological symptoms

S Göthberg[1], KE Edberg[1], SF Tang[4], S Michelsen[3], P Winberg[2], D Holmgren[1], O Miller[4], E Thaulow[3] and P-A Lönnqvist[2]

Department of Paediatric Anaesthesia and Intensive Care and Paediatric Cardiology[1], The Queen Silvia Children's Hospital, Göteborg, Sweden; Astrid Lindgren's Children's Hospital[2], Stockholm, Sweden; Rikshospitalet[3], Oslo, Norway; Royal Alexandra Hospital for Children[4], Sydney, Australia

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Inhaled nitric oxide is a potent vasodilator in acute severe pulmonary hypertension and is increasingly used as rescue treatment in intensive care algorithms aiming at reducing severe hypoxaemia in neonates and children. Although the immediate effects may seem impressive, long-term outcome regarding residual pulmonary hypertension and other sequelae has been studied in only a very few patients. The aim of the present study was to evaluate residual pulmonary hypertension, cardiopulmonary or neurological symptoms in children after treatment with inhaled nitric oxide in severely hypoxaemic and/or pulmonary hypertensive mechanically ventilated children. The study was performed in four paediatric intensive care units in university hospitals in Sweden, Norway and Australia. Patients who had received inhaled nitric oxide as part of their intensive care treatment for severe hypoxaemia and/or pulmonary hypertension, and in whom 6 mo had elapsed since treatment, were included for evaluation. Thus 36 paediatric or neonatal patients were examined for circulatory, respiratory or neurological disorders with clinical examination, echocardiography, chest X-ray and a capillary blood sample. Four patients with congenital heart disease had residual pulmonary hypertension. Nine patients were receiving bronchodilators. Sixteen patients had minor ($n = 15$) or moderate ($n = 1$) changes on a chest X-ray. One patient had a possible delay in psychomotor development.

Conclusions: In spite of the severity of their primary illness, we found that the overwhelming majority of the surviving children were asymptomatic and doing well. The few residual circulatory and respiratory symptoms could be related to the initial condition.

Key words: *Acute respiratory failure, children, congenital heart defect, follow-up, inhaled nitric oxide, pulmonary hypertension*

Sylvia Göthberg, Department of Paediatric Anaesthesia and Intensive Care, The Queen Silvia Children's Hospital, SE-416 85 Göteborg, Sweden (Tel. +46 31 343 5613, fax. +46 31 343 5880, e-mail. sylvia.gothberg@sahlgrenska.se)

In the neonatal period, persistent pulmonary hypertension of the newborn (PPHN) causes significant morbidity and mortality, especially in patients with severe meconium aspiration syndrome (MAS), congenital diaphragmatic hernia (CDH), respiratory distress syndrome (RDS) or in neonatal sepsis (1). High pulmonary vascular resistance and ventilation-perfusion mismatch accompany the acute respiratory distress syndrome (ARDS) in paediatric and in adult patients (2). Patients with congenital heart defects (CHD) with increased pulmonary blood flow may exhibit severe pulmonary hypertension owing to endothelial dysfunction (3), remodelling of the pulmonary vasculature (4) or to a decreased release of nitric oxide (NO) after operations on cardiopulmonary bypass (5–7).

Several reports have shown a reduction of pulmonary artery pressure as well as enhanced gas exchange after short-term administration of inhaled nitric oxide (iNO) to neonatal and paediatric patients (8–12). Because of its unique action as a selective pulmonary vasodilator (13), iNO has rapidly become a widespread part of the therapy for severe hypoxaemic respiratory failure and has been shown to reduce the need for ECMO in newborn patients with PPHN (14). Immediate side effects have been few (15–17), and when present relate mainly to rebound phenomena on withdrawal (18–20).

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NO and nitrogen dioxide have toxic effects on the respiratory epithelium in large doses (21, 22) and NO might have toxic effects on the endothelium after long-term exposure (23). Hypothetically, treating severely hypoxaemic patients to survival could also increase the incidence of residual lung disease or delayed psychomotor development. Although iNO has become a common treatment in neonatal and paediatric intensive care, follow-up studies have been reported in only 150 paediatric patients, in 5 studies with follow-up times from 5 mo to 4.3 y (24–28).

The aim of the present study was to perform a follow-up examination in newborns and children treated with iNO and to address the following issues:

1. Do patients, treated with iNO because of pulmonary hypertension, have residual signs of pulmonary hypertension?
2. Do patients, treated with iNO have residual signs or symptoms of airway disease?
3. Do patients, treated with iNO because of severe hypoxaemia, survive with neurological sequelae?

We hypothesized that residual pulmonary hypertension would not be common. We also hypothesized that pulmonary and neurological disorders would increase owing to increased survival of severely ill patients.

Subjects

Thirty-six patients with hypoxaemia in spite of conventional intensive care or pulmonary hypertension after corrective heart surgery using cardiopulmonary bypass were eligible for the study. The patients were recruited from four paediatric intensive care units and must have been treated with iNO for more than 30 min. At follow-up, 6 mo or more had elapsed since treatment. Patients who subsequently were treated with extracorporeal membrane oxygenation were excluded from the analysis. Median age in the study group was 17.5 mo (range 7 mo to 15.3 y of age). Sixteen patients were treated with iNO in the postoperative period after open heart surgery and 20 patients received iNO as treatment for acute respiratory failure (ARF) with a median P/F-ratio (PaO_2 (mm Hg)/FiO_2) of 45 (range 15–185). The congenital heart defects are described in Table 1. ARF was attributable either to PPHN ($n = 12$) subgrouped in the table or to ARDS ($n = 8$). The diagnoses of the patients with ARDS were pneumonia ($n = 5$), septicaemia ($n = 2$) and lung hypoplasia ($n = 1$).

At the start of treatment, 33 patients already had changes on their chest X-rays. Only three patients had a clear chest X-ray. Twenty-seven patients had evidence of pulmonary hypertension (PHT) when evaluated with echocardiography before starting iNO treatment. Seven patients did not have evidence of PHT and two patients were not or could not be evaluated before NO treatment.

Treatment with iNO commenced at a median age of 29 d (range 1 d to 14.4 y of age) for a median duration of 113 h (range 1–451 h) with a dose range of 0.3 to 80 ppm NO (AGA, AB, Lidingö, Sweden and BOC, Parramatta, Australia). This information is presented in subgroups in Table 1.

Methods

At review 6 mo or more after iNO therapy, the patients were examined for respiratory, circulatory or neurological disorders. The study was approved by the ethics committees at the participating universities and performed after parental consent.

Age, sex, weight, length and time elapsed after iNO and medication at follow-up were registered. Patient history was carefully assessed regarding weight gain, symptoms of respiratory or circulatory disease and psychomotor development. When possible, a capillary blood sample for blood gases and a haemoglobin level

Table 1. Demographic data on patients studied. Atrioventricular septal defect (AVSD), ventricular septal defect (VSD), total anomalous pulmonary venous return (TAPVR), persistent pulmonary hypertension of the newborn (PPHN), meconium aspiration syndrome (MAS), congenital diaphragmatic hernia (CDH), respiratory distress syndrome (RDS), acute respiratory distress syndrome (ARDS).

Diagnosis	No.	Age at iNO Median (range) d/mo/y	iNO duration Median (range) h	Follow-up time Median (range) mo
Congenital heart defects	16	6 mo (1 d–8.5 y)	115 (1–403)	14 (7–31)
AVSD	3	8 mo (4 mo–11 mo)	39 (1–269)	12 (10–18)
VSD	2	11 mo–8.5 y	1–403	17–31
TAPVR	2	1 d–9 d	44–185	7–12
Single ventricle	4	2.4 mo (1 d–7.5 y)	92 (50–333)	14 (8.5–17)
Combined defects	5	27 d (7 d–9 mo)	144 (40–350)	14 (10–22)
Acute respiratory failure	20	2 d (1 d–14.4 y)	113 (3–451)	13.5 (7–27)
PPHN	12	1 d (1–2 d)	109 (3–451)	14 (8–27)
MAS	8	1 d (1–2 d)	109 (3–451)	13.5 (8–26)
CDH	3	1 d (1–2 d)	143 (60–169)	17 (16–27)
RDS	1	2 d	35	8
ARDS	8	3 mo (27 d–14.4 y)	118 (22–401)	11 (7–21)
Total	36	29 d (1 d–14.4 y)	113 (1–451)	14 (7–31)

were taken. Peripheral oxygen saturation was registered with pulse oximetry.

A clinical examination for tachypnoea, retractions, clubbing and/or wheezing, and heart auscultation was performed. A simple screening test modified from Milani-Comparetti, was used for assessment of neurological development (29, 30).

An echocardiogram specifically addressed pulmonary hypertension (PHT) and was scored qualitatively as 0 (no PHT), + (signs of PHT), ++ (moderate PHT) or +++ (severe PHT). Right and left heart function was evaluated. When possible, an estimation of pulmonary artery pressure was made. The electrocardiogram (ECG) was examined for signs of right ventricular (RV) hypertrophy, RV strain, left ventricular (LV) hypertrophy and LV strain using standard criteria. A chest X-ray was qualitatively scored as 0 (clear), + (minor pathology), ++ (moderate pathology) or +++ (total consolidation). The individual physicians at the participating centres did the scoring of PHT and chest X-ray.

Results

The median follow-up time after iNO treatment was 14 mo (range 7–31 mo) (Table 1). Thirty-two patients had normal weight gain. Of those who did not, one was a conjoined twin, one patient had a neurometabolic disorder and two had short gut syndrome.

Circulatory system

The echocardiogram at follow-up was performed in 35/36 patients and revealed no evidence of PHT in 31 patients. Twenty-two of these had had PHT at the time of NO treatment, seven had not and two had not been evaluated with echocardiography before treatment. Four patients had residual PHT, with an estimated systolic pulmonary artery pressure of 40–80 mm Hg. Three of these were patients with repaired atrioventricular septal defects (AVSD) and Down's syndrome, and two of these three subsequently died, at 12 and 13 mo, respectively, after surgery and treatment with iNO. The fourth patient with residual PHT had a complex congenital heart defect corrected with a Mustard procedure, with both mitral valve and tricuspid valve insufficiency at follow-up. The scoring of pulmonary hypertension is summarized in Table 2a.

An ECG was performed in 30 patients and was abnormal in 2 patients without congenital heart disease. First-degree atrioventricular block (AV-block) was found in one patient with MAS, and signs of RV hypertrophy were found in the patient with lung hypoplasia. All other findings (2^{nd}-degree AV block ($n = 1$), RV hypertrophy ($n = 1$) and right bundle branch block ($n = 3$)) could be explained by the congenital heart disease. An ECG was not performed in six patients and routine criteria could not be applied in four patients with a pacemaker or a single ventricle.

Heart auscultation was normal in 28/36 patients. Eight patients had cardiac murmurs or clicks, explained by the underlying CHD in all but one patient, who had a diaphragmatic hernia. Oximetry was normal (> 93%) in 27 patients and was not performed in 6. Three patients had expected desaturation, 77, 84 and 90% respectively, owing to single ventricle physiology. Haemoglobin was normal in 26 patients and was not performed in 9. One patient with a single ventricle had a supernormal haemoglobin value (235 g/l).

Six patients with congenital heart disease were treated with medication daily for their circulatory disorders (e.g. anticoagulants, diuretics and vasodilators).

Respiratory system

Four patients had signs of respiratory disease at the clinical examination with tachypnoea, retractions or wheezing. Seven patients had daily bronchodilator treatment (ARF $n = 5$, CHD $n = 2$) and another two ARF patients used a bronchodilator when necessary. Sixteen patients had an abnormal chest X-ray at follow-up. Six of these patients had Down's syndrome. Two patients with clear X-rays at treatment had minor abnormalities at follow-up. The chest X-ray scoring is summarized in Table 2b.

Central nervous system

One patient, a conjoined twin, had a minor developmental delay, one patient with a neurometabolic disease and 8 patients with Down's syndrome had an expected degree of psychomotor delay. Twenty-six patients had no signs of major neurological sequelae.

Table 2a. Echocardiographic signs of pulmonary hypertension in patients studied.

	Pulmonary hypertension							
Score	at iNO					at follow-up		
Absent	7					31		
Present	27					4		
Breakdown of scores	+	+/++	++	++/+++	+++	+	++	+++
	6	1	10	1	9	0	4	
Note performed or evaluated	2					1		

Table 2b. Chest X-ray findings in the patients studied.

	Chest X-ray findings							
Score	at iNO					at follow-up		
Absent	3					20		
Present	33					16		
Breakdown of scores	+	+/++	++	++/+++	+++	+	++	+++
	12	4	11	1	5	15	1	

Discussion

Residual pulmonary hypertension at follow-up after treatment with iNO was found in 4 out of 36 examined infants, all among patients with initial congenital heart defects and none among patients with acute respiratory failure. Only four patients had signs of residual pulmonary disease at physical examination although bronchodilator medication was used by 9 (25%), and 16 patients had abnormal findings on chest X-ray. No patient had any unexpected major neurological sequelae.

An important finding in this study is that few residual respiratory, circulatory or neurological signs or symptoms were found at follow-up in 36 patients after treatment with iNO despite the severity of the primary illness. Previous follow-up studies have reported on 150 children in 5 different studies, 104 children after iNO treatment owing to PPHN (24, 25, 27, 28) and 46 children treated after cardiac surgery due to pulmonary hypertension (26). Our follow-up study adds another 36 children including some ($n = 8$) with ARDS. No patients with ARDS have been included in previous follow-up studies.

This study was only concerned with intermediate and long-term sequelae. Immediate adverse reactions during iNO treatment, such as pulmonary oedema, rebound pulmonary hypertension on withdrawal, methemoglobinaemia and increased bleeding time were not recorded in these protocols.

In two previous follow-up studies, residual pulmonary hypertension has been addressed (26, 28). In patients with congenital diaphragmatic hernia, Rosenberg found residual hypertension in 2/51 (4%) at 1 y follow-up. This is supported by our study, where no PHT was found in patients with PPHN or ARDS. In postoperative cardiac patients, Yahagi found residual PHT in 4/46 (9%) to be compared with 4/16 (25%) in patients with CHD in our study. This difference may be related to the longer follow-up time in the study by Yahagi (37 mo versus our mean follow-up time of 14 mo) or to the severity of any residual effects. Two of our patients with AVSD and progressive pulmonary hypertension died 1 y after follow-up. Other circulatory symptoms and signs (cardiac murmur, ECG abnormalities and need of pacemaker) observed in this study were few and could be related to the underlying congenital heart disease.

Rosenberg et al. found that 1/3 of their patients had a clinical diagnosis of reactive airway disease at follow-up, with chronic medication or a residual oxygen need (28). Dobyns et al. investigated the pulmonary function in 15 former PPHN patients treated with iNO. There was no altered pulmonary function in patients treated with iNO owing to severe PPHN, compared with healthy aged-matched controls (24). In our study, four patients had signs of residual pulmonary disease, two were cardiac patients and two ARDS patients. Four patients with ARDS and three patients with PPHN had bronchodilators in our study. The rate of treatment in patients with respiratory problems in our study is comparable with previous studies of paediatric patients after PPHN or ARDS (31–36). Respiratory syncytial virus infection (RSV) complicated the course of one CHD patient and was the reason for iNO treatment in another patient with ARF. These two patients have reactive airway disease and/or frequent upper and lower respiratory tract infections, which are common complications after RSV infection (37).

Rosenberg found signs of neurological sequelae in 25% at 1 y and in 21% at 2 y of age while we did not see any major neurological disorders in our study. They conclude that the neurodevelopmental outcome in their study was similar, as in patients treated with ECMO compared with conventionally treated patients. Thus it is likely that the central nervous system damage in these infants is related to the underlying disease severity (28). Another study of PPHN patients treated with iNO revealed mild conductive hearing loss at follow-up in 3/28 PPHN patients (27). Cheung et al. studied a group of 24 very low birthweight infants ($\leq$1500 g) resuscitated with iNO and reported a 58% mortality with neurological sequelae in 7 of 10 survivors (25). In our study, only one ARDS patient, a conjoined twin, showed possible neurological sequelae at the age of 14 mo. In 8 patients with Down's syndrome and in one patient with a neurometabolic disease a psychomotor delay was expected.

The optimum age for developmental assessment will vary according to the scale used and the aspect of development about which data are wanted. Eighteen patients were evaluated at 18 mo of age or less and 5 were less than 9 mo of age. With the method we used, it was possible to detect major motor sequelae (38). Such sequelae might not be consistent, and poor prognostic significance is attached to developmental tests per-

formed before the age of 18 mo. Further follow-up studies are needed to reveal psychomotor developmental disorders in these very sick children.

A potential limitation in this study is that different intensivists, cardiologists and radiologists have been involved in the clinical and radiological examination, although the protocol has been the same in all centres. The protocol was designed for use during a single follow-up visit and should recognize long-term adverse effects without harming the patients with extensive investigations using qualitative measures in circulatory, respiratory and neurological status.

In conclusion, few patients in the whole study group had residual pulmonary hypertension, which was found only in patients with congenital heart defects, 4/16 (25%). It could not be shown that pulmonary and neurological sequelae increased owing to improved survival of severely ill patients. The numbers of patients with symptoms and medication were comparable with other studies. The few circulatory, ventilatory or neurological residual symptoms found at follow-up examination could be explained by the underlying initial disease.

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