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Inhaled nitric oxide treatment of children with pulmonary hypertension after cardiac surgery

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Abstract

The presence of pulmonary hypertension in children with a congenital heart defect carries the risk of considerable problems of management immediately after corrective surgery. To evaluate whether inhaled nitric oxide (NO) complements other routine therapeutic measures to lower pulmonary artery pressure, 28 infants and children (ages, 0.85 ± 0.19 years) with this condition were studied within the first few days after surgery. Hemodynamics and/or oxygen saturations were significantly improved by NO inhalation (initial concentration, 15 ± 1.8 ppm) in 27 patients (96%). Mean pulmonary arterial pressure (PAP) declined significantly from 45 ± 5.8 to 27 ± 3.1 mmHg, whereas there were significant increases in mean systemic arterial pressure (55 ± 1.9 to 59 ± 1.8 mmHg) and arterial oxygen saturation (Sao_2, 90 ± 1.9 to 97 ± 1.1%). The changes in PAP (ED_{50}: 0.29 ± 0.07 ppm NO) and Sao_2 (ED_{50}: 0.21 ± 0.04 ppm NO) were dose-dependent with no significant difference in ED_{50} values. The NO-induced pulmonary vasodilation was independent of the concomitant reduction in arterial carbon dioxide tension. In a case-control study of a subgroup of 18 patients and 35 matched controls, inhaled NO significantly reduced the frequency of pulmonary hypertensive crises by 83% and lowered the mortality rate from 14.2% to zero. During low-dose NO inhalation there was no detectable formation of methemoglobin or significant production of nitric dioxide (NO_2), and no disturbance of platelet aggregation or leukocyte adhesion. It is concluded that in children undergoing cardiac bypass surgery, low-dose inhaled NO improves hemodynamics and oxygenation, and reduces the frequency, severity, and mortality of pulmonary hypertensive crises during perioperative intensive care. We recommend a dose range of 1–10 ppm NO for routine use, and an absolute upper dose limit of 40 ppm NO to avoid potential adverse side effects.

Keywords: Inhaled nitric oxide; Pulmonary hypertension; Pulmonary hypertensive crisis; Congenital heart disease; Cardiopulmonary bypass surgery; Postoperative intensive care

1. Introduction

Pulmonary hypertension is often present in infants and children with congenital heart defects associated with extensive left-to-right shunts. It may persist immediately after corrective surgery until the pulmonary vascular resistance has regressed sufficiently to accommodate the postoperative hemodynamic and intracardiac volume changes. During the first few days after surgery, these patients frequently develop a pulmonary hypertensive crisis (PHC), despite conventional therapy with hyperventilation, hyperoxygenation, and intravenous vasodilators. The condition continues to be a major complication of congenital heart surgery with a mortality rate ranging from 30% to 50% [19,26,31].

The purpose of this study was to determine if inhaled NO improves postoperative hemodynamics

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and oxygenation, whether it exerts its effects in a dose-dependent fashion, and whether it reduces the frequency of PHC.

2. Patients and methods

2.1. Patients

The indication for using inhaled NO was persistent postoperative pulmonary hypertension in defects with preoperative left-to-right shunts. Patients were enrolled in the study if one or more of the following criteria were met postoperatively: (1) ratio of pulmonary arterial-to-systemic arterial pressure greater than 0.4; (2) development of a PHC; (3) arterial oxygen saturations continuously lower than 90% after exclusion of other causes; and (4) need for a fractional inspiratory oxygen concentration of 1.0 for more than 48 h. Twenty-eight infants and children met these criteria. Fifteen patients had a ventricular septal defect (VSD) or an atrial septal defect (ASD), five had an atrioventricular septal defect (AVSD), four had a common arterial trunk, one patient had aortic atresia with a previously ductal dependent systemic circulation, and three had other defects with an intracardiac left-to-right shunt.

A PHC was defined as a typical sequence beginning with an acute increase of pulmonary arterial pressure (PAP), with decreases of arterial oxygen saturation (Sao_2) and systemic arterial pressure (SAP), and a need to provide manual hyperventilation or to use vasodilating drugs [19,26,57].

To determine if inhaled NO reduces the frequency of PHCs, a case-control study was performed using 53 infants and children who had corrective cardiac surgery at our institution. The study group, Group III, consisted of 18 patients with pulmonary hypertension who had no residual defects after surgical correction of a VSD, ASD or AVSD. Their mean age was 0.89 ± 0.18 years and they had a mean preoperative PAP/SAP ratio of 0.82 ± 0.06. The controls consisted of 35 patients matched for comparable age (mean, 0.96 ± 0.13 years), preoperative hemodynamic parameters (mean PAP/SAP ratio, 0.82 ± 0.04), and heart defects operated upon during a 3-year period before NO was used in postoperative management at our institution. The control patients were further divided into two subgroups. Group I consisted of 18 patients who had no obvious postoperative pulmonary hypertension with PAP/SAP ratios consistently less than 0.4. Group II contained 17 patients who had postoperative pulmonary hypertension with PAP/SAP ratio ≥ 0.4. In all of the study and control patients, hemodynamic and respiratory measurements were averaged within each 12-h interval of care during the first 5 postoperative days. As soon as the patients were admitted to the intensive care unit, the Pediatric Risk of Mortality score (PRISM) was determined to compare the status of study and control patients [39].

The ethics committee of the University of Tuebingen approved the study and informed consent was obtained from the parents.

2.2. Inhaled NO

Nitric oxide (Messer-Griesheim, Duisburg, Germany) was introduced as a NO/NO_2 gas mixture into the afferent limb of the ventilator circuit, close to the endotracheal tube, and was continuously measured as previously described [6]. The available hemodynamic and oxygenation parameters were measured and recorded during inhalation of 0, 1, 5, 10 and 40 ppm NO for 10 min each. Thereafter inhalation was continued with 1–10–30 ppm NO as required to obtain stable hemodynamics and gas exchange. With clinical improvement, the NO concentration was reduced daily and finally discontinued. To test the reactivity of the pulmonary vasculature to carbon dioxide, a daily NO exclusion test was performed in 6 patients and was complemented with a hyperventilation test in which the peak inspiratory pressure was increased by 5 cmH_2O for 10 min.

The system for using inhaled NO was reviewed and approved by the Technical Surveillance Association (TUV Suedwest, Stuttgart, FRG).

2.3. Hemodynamics and gas exchange

Routine postoperative hemodynamic monitoring included heart rate, respiratory rate, arterial oxygen saturation, systemic arterial pressure and central venous pressure. In most patients, indwelling catheters were surgically placed in the pulmonary artery and the left atrium to monitor pressures. All of the available parameters were recorded continuously using the Intensive Care Monitoring System (MERLIN/MARS, Hewlett Packard, Boblingen, FRG). Cardiac output (CO) was determined by the Fick principle and indexed to body surface area (CI). Pulmonary vascular resistance index (PVRI), systemic vascular resistance index (SVRI), intrapulmonary shunting (Qs/Qt), and arterial oxygen content (cO_2) were calculated using standard equations.

2.4. Statistical analysis

Results are presented as the mean $\pm$ S.E.M. Statistical analysis was performed using the PC-based SAS 6.03 software package (SAS Institute, Cary, USA). The normal distribution of each parameter was verified by univariate analysis of variance. Analysis of variance with adjustments for multiple comparisons

(Bonferroni *T*-tests) and analysis of variance for repeated measures were used for statistical comparison. Logistic dose-response curves with the parameters ED_{50} and E_{MAX} were fitted to the data for PAP and Sa_{O_2} separately. A *P*-value of $P < 0.05$ was considered statistically significant.

3. Results

3.1. Hemodynamics and gas exchange

Inhaled NO acutely improved pulmonary and systemic hemodynamics, as well as pulmonary gas exchange, in 27 of 28 patients (96%). The only patient in this group who did not respond was a 3-week-old newborn who had corrective surgery for a common arterial trunk. The reason for the unresponsiveness was not known. In the other 27 patients, pulmonary arterial pressure decreased significantly from 45 ± 5.8 to 27 ± 3.1 mmHg, due to a reduction of pulmonary vascular resistance by approximately 48% (Table 1). In contrast, systemic arterial pressure increased significantly from 55 ± 1.9 to 59 ± 1.8 mmHg and the systemic vascular resistance remained constant. The changes are related to a small, statistically insignificant, rise in cardiac index. However, an improved cardiac output might be inferred from the significant rise in mixed venous oxygen saturation (Table 1). A reduced afterload of the subpulmonary ventricle and improved pulmonary perfusion during inhaled NO is indicated by a slight reduction in central venous pressure and a small increase in left atrial pressure.

Inhaled NO led to significant increases in arterial oxygen tension and saturation, and a decrease in arterial carbon dioxide tension (Pac_{O_2}) due to a reduction in intrapulmonary right-to-left shunting, as indicated by a lower Qs/Qt (Table 1).

The acute effects of inhaled NO on hemodynamics and oxygenation clearly persisted for a prolonged period (Fig. 1). The slight increase in mean SAP demonstrated earlier is not seen in this figure because after an initial improvement it was possible to reduce the dose of intravenous catecholamines. The daily NO exclusion tests showed that the magnitude of the benefits of NO decreased daily as the patients became increasing more stable after the operation.

3.2. Hyperventilation vs. inhaled NO

Low arterial carbon dioxide tension, with its associated alkalosis, leads to a decrease in pulmonary arterial pressure. Since inhaled NO also reduces arterial carbon dioxide tension, we asked whether the reduction in pulmonary pressure from NO is the result of its effect on carbon dioxide. The correlation between carbon dioxide tension and the PAP/SAP ratio, with and without NO therapy, was studied in one infant with persistent pulmonary hypertension after closure of a VSD and ASD (Fig. 2A). When NO was used, the slope of the line of regression between both parameters was much lower and shifted to the right. This indicates a reduced sensitivity of the pulmonary vasculature to changes in carbon dioxide tension. Further evidence for this is seen by an analysis of the hyperventilation and NO-exclusion tests in six patients (Fig. 2B). The reduction in pulmonary pressure induced by inhaled NO (+NO) is greater than expected if it were solely the result of the NO-related decrease in arterial carbon dioxide tension.

Table 1
Hemodynamics and gas exchange before and 20 min after beginning NO inhalation in 28 infants and children with persistent pulmonary hypertension after cardiopulmonary bypass surgery for congenital heart disease

Parameters	Before NO	During NO (15 ± 1.8 ppm)
Heart rate (bpm)	144 ± 4.5	143 ± 4.6
SAP (mmHg)	54.8 ± 1.85	59.1 ± 1.82*
PAP (mmHg)	44.5 ± 5.84	26.9 ± 3.12*
PAP/SAP	0.73 ± 0.08	0.42 ± 0.04*
CVP (mmHg)	11.0 ± 0.55	10.3 ± 0.56
LAP (mmHg)	10.6 ± 0.91	11.07 ± 0.87
CI ($l/min/M^2$)	3.18 ± 0.23	3.37 ± 0.25
SVRI ($dyn/M^2/cm^5$)	1237 ± 92	1314 ± 97
PVRI ($dyn/M^2/cm^5$)	912 ± 201	406 ± 107*
Sa_{O_2} (%)	89.6 ± 1.91	96.8 ± 1.09*
Pa_{O_2} (mmHg)	84.3 ± 9.80	140.33 ± 15.09*
Pac_{O_2} (mmHg)	33.6 ± 1.01	31.5 ± 1.05*
c_{O_2} (ml O_2/ml)	16.3 ± 0.51	17.4 ± 0.47*
Sv_{O_2} (%)	62.4 ± 3.22	70.6 ± 2.33*
Qs/Qt (%)	31.8 ± 3.40	22.7 ± 2.65*
MetHb (%)	0.77 ± 0.03	1.57 ± 0.14*

The ventilator settings were kept constant between the two measurements: peak inspiratory presure 21.5 ± 0.93 cmH_2O, mean airway pressure 9.26 ± 0.37 cmH_2O, positive end-expiratory pressure 3.86 ± 0.27 cmH_2O, and Fi_{O_2} 0.81 ± 0.04.
SAP: mean systemic arterial pressure; PAP: mean pulmonary arterial pressure; CVP: central venous pressure; LAP: left atrial pressure; CI: cardiac index; SVRI: systemic vascular resistance index; PVRI: pulmonary vascular resistance index; Sa_{O_2}: arterial oxygen saturation; Pa_{O_2}: arterial oxygen tension; Pac_{O_2}: arterial carbon dioxide tension; c_{O_2}: arterial oxygen content (at two different methemoglobin concentrations); Sv_{O_2}: mixed venous oxgen saturation; Qs/Qt: intrapulmonary right-to-left shunt; MetHb: methemoglobin concentration.
* Statistically significant difference ($P < 0.05$).

3.3. Clinical results

Nitric oxide therapy was used for 1–8 days (mean 4.3 ± 0.4 days). The initial NO dose was 15 ± 1.8 ppm, which was reduced daily. In 25 patients, NO therapy was discontinued when the daily exclusion tests showed it was not needed. Several days after stopping NO, two of these patients died, one from sepsis and

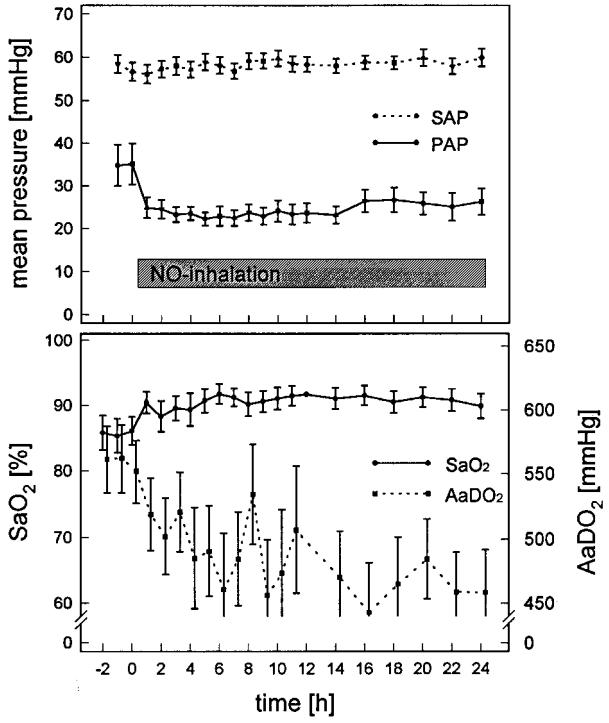

Fig. 1. Effect of inhaled nitric oxide (NO) during the first 24 h of its use in 25 infants and children on the mean systemic arterial pressure (SAP), mean pulmonary arterial pressure (PAP), arterial oxygen saturation (Sao_2), and alveoloarterial oxygen difference ($AaDo_2$). Each value represents the 1-h or 2-h average of measurements.

the other from multiple organ failure following reoperation. Three other patients died from sepsis or multiple organ failure in spite of continued NO therapy.

3.4. Dose-response of NO

The data of 29 dose-finding phases in 20 patients were used to construct dose-response curves for pulmonary arterial pressure and arterial oxygen saturations (Fig. 3). The main effect of NO on both parameters occurred with doses between 0 and 5 ppm (Fig. 3A). After fitting this data to logistic dose-response curves, the calculated ED_{50} values were 0.29 ± 0.07 ppm for PAP and 0.21 ± 0.04 ppm for Sao_2. The corresponding ED_{95} values were 5.4 ± 1.3 ppm for PAP and 3.3 ± 1.2 ppm for Sao_2. These dose responses are in accord with clinical experiences with these types of patients who have a near-maximal effect of NO below a dose of 10 ppm.

3.5. Case-control study

Between the NO-treated patients and the controls, no statistically significant differences were detected for the measured preoperative and postoperative

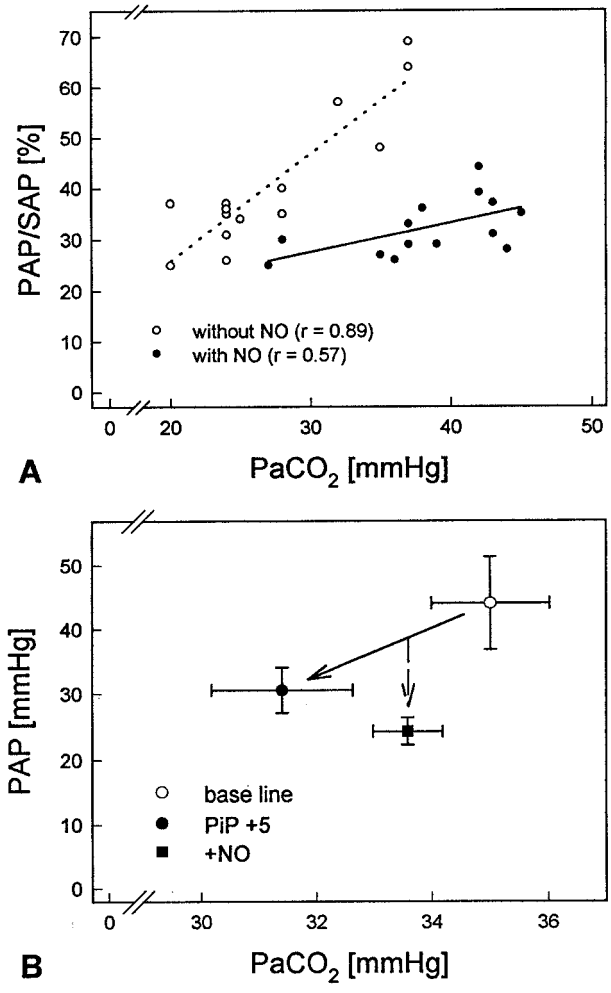

Fig. 2. (A) Effect of hyperventilation (low Pao_2 levels) on pulmonary arterial pressure (PAP), expressed as percent of systemic arterial pressure (PAP/SAP) in an infant treated after closure of a VSD and ASD without NO (○) and with NO (●). Inhaled NO induces a flattening and rightward shift of the regression line. (B) Results of hyperventilation and NO-exclusion tests in six children. The additional effect of NO on PAP cannot be attributed to the NO-mediated reduction in $Paco_2$, as indicated by the broken arrow. (○) Base line: normal ventilation 'without' NO; (●) PiP + 5: hyperventilation with increased peak inspiratory pressure 'without' NO; (■) +NO: normal ventilation 'with' NO treatment.

parameters or in the postoperative PRISM scores. Comparison of the control patients with postoperative pulmonary hypertension, who did not receive NO (Group II), and the study patients with postoperative pulmonary hypertension who received NO (Group III), showed that pulmonary arterial pressure was significantly lower in the patients treated with NO (Table 2). Therefore, hyperventilation with hypocarbia and artificial hyperoxygenation (as indicated by $Paco_2$, Fio_2 and Pao_2 values) had to be significantly less in the treated patients.

Moreover, these Group III patients had a significantly negative fluid balance. Since they also received

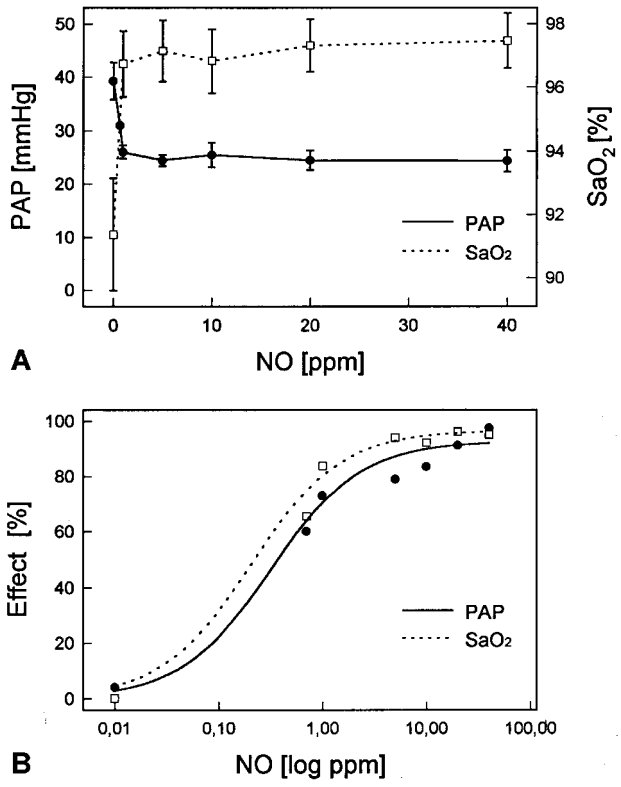

Fig. 3. (A) Changes in pulmonary arterial pressure (PAP) and arterial oxygen saturation (Sa_{O_2}) during inhalation of NO in 29 dose-finding phases in 20 children. (B) Constructed dose-response curves fitting the data to a logistic function demonstrating the effect (%) of inhaled NO on original data for PAP (●) and Sa_{O_2} (□).

greater diuretic therapy with increased doses of furosemide (Table 2), further statistical analysis was performed to evaluate the influence of different parameters on fluid balance. Multiple regression analysis revealed that the increased urine output was dependent on systemic arterial pressure, peak inspiratory pressure, and greater doses of furosemide and theophyline, and also related to the use of NO.

After beginning NO inhalation, the frequency of PHC was significantly reduced by 83%. Of the 18 patients who were treated with NO, only four had a PHC (22%), whereas this complication was observed in 19 of the 35 control patients (54%) who did not receive NO (Fig. 4). The mortality rate for PHCs was 14.2% in patients not treated with NO and there were no deaths in those who received NO.

4. Discussion

In most infants and children with an intracardiac left-to-right shunt and pulmonary hypertension, pulmonary arterial pressure returns to normal immediately after the defect is closed. However, pulmonary hypertension may persist after surgery in children with structural changes of the pulmonary vascular bed, elevated pulmonary vascular resistance before surgery, prolonged cardiopulmonary bypass, inadequate analgesia or sedation, insufficient ventilation, and with other rarer abnormalities. These patients, and even those with normal pulmonary artery pressure after surgery, may have a PHC triggered by stress, hypoxemia, and hypercapnia, among other conditions. As illustrated in Fig. 5, the first event in the crisis is an increase in pulmonary vascular resistance leading to an abrupt increase in pulmonary arterial pressure. Then right ventricular output, left atrial pressure, and cardiac output are decreased, producing a further increase in pulmonary vascular resistance. The reduction in cardiac output decreases systemic arterial pressure and impairs coronary perfusion, adding to the biventricular myocardial dysfunction already affected by a lower arterial oxygen saturation.

4.1. Therapeutic aspects

Pulmonary hypertension can be treated by hyperoxygenation ($Pa_{O_2} > 150$ mmHg), hyperventilation (Pa_{CO_2} 20–30 mmHg [34]), and with vasodilators such as prostacyclin, prostaglandin E_1, tolazoline, enoximone, and sodium-nitroprusside [46]. However, each of these measures has disadvantages. The inspiration of a high concentration of oxygen over a prolonged time may injure the lining of the lung, low carbon dioxide concentration produced by hyperventilation can markedly reduce cerebral arterial perfusion [5,41], and intravenous vasodilators are non-selective drugs that also dilate systemic arterial vessels with the potential for impaired myocardial perfusion [46]. In experimental animal studies, Vlahakes et al. [54] showed that a right ventricle subjected to a markedly elevated pressure load failed when the systolic PAP/SAP ratio was 1.0, and the right ventricular free wall became ischemic, whereas the left ventricular myocardium was not affected. Right ventricular function and regional myocardial blood flow improved when the PAP/SAP ratio was decreased to 0.81 by raising systemic arterial pressure and by increasing coronary perfusion pressure with infusion of phenylephrine. In part, this improvement may be related to the so-called 'Gartenschlaucheffekt' [33], i.e. an improvement of cardiac contractility by stretching of the myocardial vasculature caused by increased coronary perfusion pressure.

The goals for treating pulmonary hypertension, therefore, should be to reduce pulmonary pressure, but also to increase the PAP/SAP ratio. This can be accomplished by the use of inhaled NO, which influences the pathophysiology of pulmonary hypertension at two sites. It selectively dilates the pulmonary vascular bed, improving right ventricular performance, car-

Table 2
Postoperative 5-day mean values of hemodynamic and respiratory parameters in 53 infants and children with a left-to-right shunt defect and preoperative pulmonary hypertension [treatment with and without nitric oxide (NO) after cardiopulmonary bypass surgery in patients with and without postoperative pulmonary hypertension (PH)]

Parameters	Group I (no PH)	Group II (PH)	Group III (PH and NO)
Number of patients	18	17	18
Nitric oxide (ppm)	0	0	4.75 ± 0.47
Heart rate (bpm)	129 ± 1.6	133 ± 1.2	135 ± 1.4
SAP (mmHg)	66.1 ± 0.8	65.7 ± 0.49	61.7 ± 0.60**
PAP (mmHg)	21.6 ± 0.8	32.7 ± 0.61*	28.0 ± 0.96**
PAP/SAP	0.31 ± 0.011	0.49 ± 0.01*	0.43 ± 0.01**
Fio_2	0.65 ± 0.02	0.75 ± 0.014*	0.62 ± 0.017**
Pao_2 (mmHg)	137 ± 5.7	140.33 ± 15.09*	131 ± 4.54**
$Paco_2$ (mmHg)	33.3 ± 0.5	31.5 ± 1.05*	34.8 ± 0.44**
$AaDo_2$ (mmHg)	300 ± 16.7	347 ± 10.9*	298 ± 12.5**
PiP (cmH_2O)	21.7 ± 0.4	22.3 ± 0.4	20.5 ± 0.3**
PEEP (cmH_2O)	2.36 ± 0.07	2.18 ± 0.04	3.7 ± 0.07**
Fluid balance ($ml/M^2/12$ h)	$+88 \pm 25$	$+47 \pm 16$	-121 ± 28**
Furosemide (mg/kg/day)	1.73 ± 0.14	1.83 ± 0.13	3.22 ± 0.23**
Epinephrine (μg/kg/min)	0.030 ± 0.017	0.093 ± 0.05	0.046 ± 0.02**
Dobutamine and dopamine (μg/kg/min)	3.33 ± 0.29	3.61 ± 0.32	4.03 ± 0.33**

SAP: mean systemic arterial pressure; PAP: mean pulmonary artery pressure; Fio_2: fractional inspired oxygen; Pao_2: partial arterial oxygen tension; $Paco_2$: partial arterial carbon dioxide tension; $AaDo_2$: alveoloarterial oxygen difference; PiP: peak inspiratory pressure; PEEP: positive end-expiratory pressure.
* Statistically significant difference between groups I and II ($P < 0.05$).
** Statistically significant difference between groups II and III ($P < 0.05$).

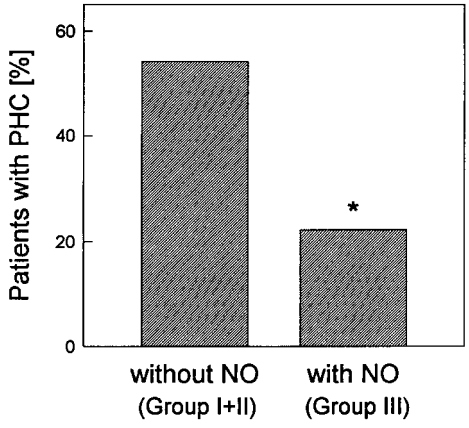

Fig. 4. Proportion (%) of patients in the case-control study with at least one pulmonary hypertensive crisis (PHC) during the first 5 postoperative days without NO treatment (Groups I and II) and with NO treatment (Group III). * Statistically significant difference ($P < 0.05$).

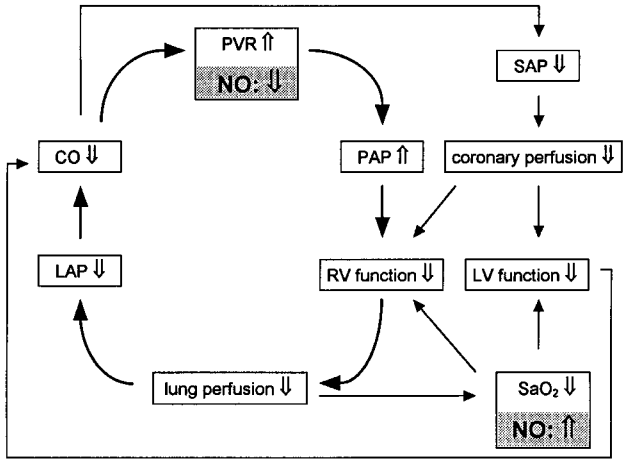

Fig. 5. Schematic diagram illustrating the pathophysiology of a pulmonary hypertensive crisis (PHC) and the two main effects of inhaled NO in treating it. PVR: pulmonary vascular resistance; PAP: pulmonary arterial pressure; SAP: systemic arterial pressure; RV: right ventricle; LV: left ventricle; Sao_2: arterial oxygen saturation; LAP: left atrial pressure; CO: cardiac output; ⇓: decrease; ⇑: increase.

diac output, and systemic arterial pressure, and it also increases oxygenation and carbon dioxide emission by reducing the postoperative pulmonary ventilation–perfusion mismatch [42]. In contrast, intravenous vasodilators can increase intrapulmonary shunting, leading to clinical instability [37]. During NO inhalation patients can be ventilated normally, preserving cerebral perfusion, as shown in one infant who had a severe PHC successfully treated by resuscitation using mechanical ventilation with NO [5].

The selective action of inhaled NO on hemodynamics has also been demonstrated in children with congenital heart disease during preoperative cardiac catheterization [40], in patients after heart transplantation [21], and in newborns with persistent fetal circulation [22]. In children with severe postoperative pulmonary hypertension, Goldman et al. [16] preferred inhaled NO to intravenous prostacyclin because of its higher efficacy and selectivity. Inhalation

of aerosolized prostacyclin, proposed as an alternative to NO, may also produce undesirable reductions in systemic arterial resistance and pressure [45].

The mechanisms for pulmonary vasodilation from hyperventilation and hyperoxygenation remain unclear. Endogenous NO may be involved with the vasodilation produced with high concentrations of inspired oxygen [48]. Another stimulus may be the reduced concentration of hydrogen ions [34] or a lower carbon dioxide tension. Our data suggest that a fall in arterial carbon dioxide tension by 10.3% during hyperventilation is more important than the minor increase in arterial pH by 0.9%. We also showed that inhaled NO dilates the pulmonary vascular bed, independent of changes in carbon dioxide tension, and that it attenuates the reactivity of the pulmonary vasculature to carbon dioxide. Sandor et al. [44] found a similar phenomenon in the cerebral vascular bed.

Analysis of the dose-response relationship between NO and pulmonary arterial pressure and arterial oxygen saturation showed (Fig. 3A) that a near-maximal effect of inhaled NO was achieved within a concentration range from 5 to 10 ppm. This is in agreement with experimental animal studies which demonstrated a maximal relaxation of isolated pulmonary artery strips at 10 ppm [18]. However, Gerlach et al. [14] and Demirakca et al. [12] postulated that the effect on pulmonary arterial pressure occurred at higher concentrations of NO (macroselectivity) than did its effect on oxygen saturation (microselectivity). This discrepancy and the different ED_{50} values observed might be related to differences in the patient populations studied. While looking at patients with adult respiratory distress syndrome, Gerlach et al. [14] found an ED_{50} of 2–3 ppm for PAP and 0.1 ppm for PaO_2. In contrast, data in our children with pulmonary hypertension from a congenital heart defect indicated an ED_{50} of 0.29 ppm for PAP and 0.22 ppm for PaO_2.

Our case-control study demonstrated that NO inhalation therapy led to a sustained improvement in the postoperative course of infants and children with persistent pulmonary hypertension after surgical correction of defects with a left-to-right shunt. These patients were hemodynamicly more stable and much more tolerant of different therapeutic and medical care measures. Although intermittent postoperative increases in pulmonary arterial pressure were not completely abolished, the episodes were markedly reduced by inhaled NO. The reason for the increase in pulmonary pressure and pulmonary dysfunction seen in some patients within 24 h after surgery seems to be the result of the trauma of extracorporeal circulation and to continuous ventilation with relatively high concentrations of oxygen. Other causes might be the postoperative activation of the complement cascade [47], with increased adhesion of leukocytes [13,23], subsequent sequestration of leukocytes in the capillaries, and damage to endothelial cells [9,10]. Because a continuous release of EDRF/NO seems necessary to establish a low pulmonary vascular resistance [7,8,11], damage to the endothelium reduces NO formation and results in an increase in pulmonary vascular resistance and pulmonary arterial pressure. Most interestingly, elevated pulmonary arterial pressure returned to normal within 48–60 h after operation in patients who received NO, but it persisted in patients without NO [3]. This indicates a beneficial effect of NO on the recovery of impaired respiratory and endothelial functions, possibly related to reductions in pulmonary capillary pressure and transvascular fluid filtration, and hence to a reduction of extravascular lung water [2]. An improved clearance of lung water during NO inhalation has also been shown experimentally in newborn lambs with persistent pulmonary hypertension [58].

More important than the decrease in pulmonary arterial pressure alone is the reduction in the frequency of PHC seen with NO treatment. This beneficial effect was assumed by Journois et al. [20], but so far, it has not been verified statistically. Hopkins et al. [19] found that a PHC occurred in 55% of patients postoperatively, with a mortality rate of 54%. Comparable results were reported by Lesche [26], a member of our group, with a PHC risk of 50% and a mortality rate of 32%. Matsumoto et al. [31] found that 18% of patients with a postoperative PAP/SAP ratio greater than 0.7 developed a PHC after surgery with a mortality rate of 33%. If these studies are aggregated, patients with a postoperative PAP/SAP ratio greater than 0.7 had a mortality rate from a PHC of 17%. Moreover, since inhaled NO reduced the number of patients who develop a PHC from 54% to 22%, its use may result in a potential decrease in the mortality rate from 17% to 7%. And moreover, this improvement in outcome was even exceeded in our case-control patients by the observed reduction in mortality from 14% to zero.

An increase in urine output during NO therapy was also found by Journois et al. [20]. The mechanisms responsible for this have not been elucidated. Important factors might be the increase in cardiac output and systemic arterial pressure, producing an increased renal perfusion pressure. A multiple regression analysis indicated that NO itself was an independent factor. It is hypothesized, therefore, that the effect of NO on urine output is specific and independent from its hemodynamic and pulmonary effects. Such an effect might be mediated by an increase in plasma cyclic guanosine monophosphate (cGMP), as documented by Wessel et al. [56] after inhalation of NO for 15 minutes. According to experimental studies in rats by

Stasch et al. [49], cGMP plays a major role as a humoral factor and transmitter of the diuretic and natriuretic effects of the atrial natriuretic peptide. After administration of acetylcholine, which induces a release of NO from the vascular endothelium, Tolins et al. [53] found an increase in renal plasma flow due to renal vasodilation, as well as an increased excretion of cGMP. These effects could be blocked by the NO antagonist, L-NMMA. It is interesting to note that in the 1930s ammonium *nitrate* was used as a diuretic [52].

4.2. Toxicological aspects

Inhaled NO diffuses from the alveolar space into the pulmonary vascular smooth muscle cell and increases cGMP by activating guanylate cyclase to produce vasodilation [32]. When NO reaches the blood stream, it is inactivated within seconds by reduced hemoglobin. In sheep hemoglobin, this reaction was found to be 5–20 times faster than the reaction of hemoglobin with oxygen [15]. The resulting nitrosylhemoglobin is quickly converted to methemoglobin, thereby forming nitrite and nitrate [30]. The rapid binding with hemoglobin is the physiological basis for the selective action of inhaled NO on the pulmonary vascular bed. Since the methemoglobin concentration remained at approximately 1.6% in our patients, the oxygen transport capacity of the blood was not significantly decreased. Actually, oxygen transport was increased by the rise in arterial oxygen saturation. As shown previously [3], there was no significant difference in the increase in methemoglobin concentration in newborn infants (from 0.88 to 1.34%) and in children older than 28 days (from 0.74 to 1.34%).

Depending on the inspiratory oxygen concentration and its initial concentration, NO is oxidized to NO_2. Using our inhalation equipment, with introduction of NO close to the endotracheal tube, and an inspired oxygen concentration above 0.95, the formation of NO_2 amounts to $1.14 \pm 0.11\%$ of the NO concentration [6]. Using an upper-dose limit of 40 ppm, a maximal NO_2 concentration of 0.45 is to be expected, which is well below the relevant toxic concentration [1,6,50,51,55].

Recent studies have demonstrated that NO reduces platelet aggregation by inducing an increase in platelet cGMP content, causing a decrease of intracellular calcium availability [17]. It has been shown, moreover, that expression of the CD41a receptor on the platelet surface, responsible for platelet aggregation, accurately reflects the dose-dependent inhibition of platelet aggregation by NO [4]. However, the doses required to reduce platelet aggregation or receptor expression were in the range of 0.18 μM to 1.50 μM NO [4,38], which is approximately equivalent to 90–700 ppm NO in aqueous solutions. Since the doses of NO recommended for clinical use are much lower (1–10 ppm), it is reasonable that no alterations were found in the natural course of changes in platelet receptor expression after cardiopulmonary bypass surgery [4]. It was concluded that corresponding platelet functions such as aggregation and adhesion are not disturbed by NO in this dose range. This is in contrast to studies of Samama et al. [43] that measured a decrease in platelet aggregation by approximately 46% in six patients with acute respiratory distress syndrome treated with inhaled NO. However, this study has some potential errors, e.g. the bleeding time remained within the normal range in these patients, and during NO inhalation variations did not correlate with measured alterations of platelet aggregation.

Nitric oxide reduces the adhesion of leukocytes at the vascular endothelium and may thereby alter the inflammatory response [27–29]. This might be an important effect of inhaled NO after cardiopulmonary bypass surgery, since these patients already show a slight, temporary immunosuppression [35]. The adhesion molecules, CD11 and CD18, are responsible for the binding of leukocytes to endothelial cells at the CD54 receptor. This binding is part of the so-called adhesion cascade, an important mechanism in the inflammatory response. However, the adhesion cascade increases capillary leakage and promotes the development of tissue edema after cardiopulmonary bypass surgery [13,24]. In addition to the upregulation of these adhesion molecules, the extracorporeal circulation induces the release of Interleukin-8 (IL-8), Tumor Necrosis Factor-α (TNF-α) and leukocyte elastase [13], and it activates neutrophil granulocytes [36] and complement by the alternative pathway [47]. Craddock et al. [9,10] related the complement activation to increased pulmonary arterial pressure, impaired oxygenation, histological evidence of sequestration of leukocytes in the capillaries, and damage to the endothelium. Our own in vitro experiments [23] showed a significant reduction in expression of the adhesion molecules CD11a, CD11b, and CD18 on lymphocytes and granulocytes with NO concentrations greater than or equal to 100 ppm ($\cong 0.2$ μM). In our patients who did not receive NO, studies showed that the expression of CD11a, CD11b, and CD18 was increased immediately after cardiopulmonary bypass, but declined to baseline or below baseline values in the next few days. In our other patients treated with NO postoperatively, a comparable expression of the adhesion molecules was seen, with no significant differences in patients not treated with NO. These data support the notion that, as with its effect on platelet aggregation, NO reduces the expression of CD11 and CD18 at much higher concentra-

Table 3
Possible indications for the use of inhaled nitric oxide in infants and children with a congenital heart defect

Main clinical problem	Examples
Increased pulmonary vascular resistance	Preoperative testing of the reactivity of the pulmonary vascular bed in patients with pulmonary hypertension
	Postoperative persistent pulmonary hypertension after corrective surgery of defects with left-to-right shunts
	Postoperative treatment after Fontan-type operations
Low arterial oxygen saturations	Reduced lung perfusion in patients with a left-to-right shunt lesion
	Ventilation–perfusion mismatch
Combination of both	Persistent pulmonary hypertension of the newborn (PHN)
	Acute respiratory distress syndrome

tions than those used for inhalation therapy [23]. Using an ischemia/reperfusion model in the canine heart, Lefer et al. [25] showed that the NO-donor SPM-5185 diminished the adhesion of neutrophils at the coronary endothelial cell and reduced the size of myocardial necrosis. This effect was obtained with a dose of 0.5 μM of the NO-donor. The dose for clinical use of inhaled NO (10 ppm $\cong$ 0.05 μM), however, is approximately 10 times less than this. Therefore, the inflammatory response that is directed against infection and also causes the reperfusion injury after cardiopulmonary bypass surgery, does not seem not to be affected by low-dose inhaled NO.

4.3. Recommendations for the use of inhaled NO

Currently, inhaled NO is not approved for use in patients. Its use, therefore, should be restricted to clinical studies approved by a local ethics committee. In each case, a clear indication should be given, and patients, parents, or care-givers must provide informed consent. From a pathophysiologic standpoint, inhaled NO seems to be useful in the several clinical conditions listed in Table 3.

Because of a shorter time response to changes in dose and a lower formation of nitrogen dioxide, we prefer to have the NO gas introduced close to the endotracheal tube. The NO concentration should be monitored continuously and the methemoglobin concentration should be measured at least once a day. From our clinical experience and the dose-response relationships, we recommend a starting dose of 10–20 ppm NO, with reduction to 1–10 ppm during the next few hours. In most patients with persistent postoperative pulmonary hypertension, a stepwise reduction in dose and final discontinuation is possible within a few days. The upper dose limit at our institution is 40 ppm NO, which should not be exceeded, based on the results of dose-response studies and because of toxic complications.

5. Conclusions

In children with congenital heart defects and pulmonary hypertension, low-dose inhaled NO improves hemodynamics and oxygenation after corrective heart surgery, and it significantly reduces the frequency, severity, and mortality of pulmonary hypertensive crises during postoperative intensive care. We recommend a dose range of 1–10 ppm NO for routine use and an absolute upper dose limit of 40 ppm NO to avoid potential adverse effects such as methemoglobinemia, nitric dioxide formation, and disturbances of platelet aggregation and leukocyte adhesion.

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