Volume 113 Number 3 March 1997

The Journal of
THORACIC
AND
CARDIOVASCULAR
SURGERY

SURGERY FOR CONGENITAL HEART DISEASE

INHALED NITRIC OXIDE IN PATIENTS WITH CRITICAL PULMONARY PERFUSION AFTER FONTAN-TYPE PROCEDURES AND BIDIRECTIONAL GLENN ANASTOMOSIS

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Objective: **The aim of this study was to evaluate the effects of inhaled nitric oxide in patients with critical pulmonary perfusion after Fontan-type procedures and bidirectional Glenn anastomosis.** ***Methods:*** **Inhaled nitric oxide (mean 4.1 ± 0.7 ppm, 1.5 to 10 ppm) was administered in 13 patients (mean age 5.6 ± 1.6 years, 1.5 to 17 years) with critical pulmonary perfusion (central venous pressure >20 mm Hg or transpulmonary pressure gradient >10 mm Hg) in the early postoperative period after total cavopulmonary connection ($n = 9$) or after bidirectional Glenn anastomosis ($n = 4$).** ***Results:*** **In patients after total cavopulmonary connection inhaled nitric oxide therapy decreased central venous pressure by 15.3% ± 1.4% ($p = 0.0001$) and transpulmonary pressure gradient by 42% ± 8% ($p = 0.0008$) and increased mean systemic arterial and left atrial pressures by 12% ± 3.6% ($p = 0.011$) and 28% ± 8% ($p = 0.007$), respectively. Arterial and venous oxygen saturations improved by 8.2% ± 1% ($p = 0.005$) and 14% ± 4.3% ($p = 0.03$), respectively. In patients after bidirectional Glenn anastomosis inhaled nitric oxide therapy resulted in a decrease of central venous pressure by 22% ± 1% and of the transpulmonary pressure gradient by 55% ± 6% and improved arterial and venous oxygen saturations by 37% ± 29% and 11% ± 3%, respectively. Mean systemic arterial and left atrial pressures remained nearly unchanged. No toxic side effect was observed in**

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Received for publication April 4, 1996; revisions requested May 24, 1996; revisions received Sept. 16, 1996; accepted for publication Sept. 20, 1996.

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J Thorac Cardiovasc Surg 1997;113:435-42

0022-5223/97 $5.00 + 0 **12/1/78169**

The Journal of Thoracic and Cardiovascular Surgery
March 1997

any patient. *Conclusion:* Inhaled nitric oxide may play an important role in the management of transient critical pulmonary perfusion caused by reactive elevated pulmonary vascular resistance in the early postoperative period after Fontan-type operations and bidirectional Glenn anastomosis. (J Thorac Cardiovasc Surg 1997;113:435-42)

Recently, inhaled nitric oxide (NO) has been reported as a selective pulmonary vasodilator in different experimental models of pulmonary hypertension.[1-3] Clinical studies have demonstrated that inhaled NO decreased elevated pulmonary artery pressure, pulmonary vascular resistance (PVR), and ventilation-perfusion mismatch in adults with adult respiratory distress syndrome,[4] in neonates with persistent pulmonary hypertension[5, 6] or with severe hypoxemic respiratory failure,[7] and in children with congenital heart disease complicated by pulmonary hypertension.[8] Inhaled NO even in low doses has been shown to reduce elevated pulmonary artery pressure and PVR in infants and children with severe pulmonary hypertension after cardiac operations without relevant negative side effects on systemic circulation.[9-11]

In patients after Fontan-type operations or bidirectional Glenn anastomosis pulmonary perfusion and consequently cardiac output are critically dependent on low PVR and normal systemic ventricular function.[12-15] In particular, in the early postoperative period even a small reactive increase of PVR may cause deleterious systemic venous hypertension associated with resistant low cardiac output syndrome despite a technically successful operation.[16]

Previously, only a few cases of inhaled NO treatment after Fontan operations[17-19] and bidirectional Glenn anastomosis[20] have been reported. We present our experience with inhaled NO in a series of patients with critical pulmonary perfusion in the early postoperative period after Fontan-type procedures and bidirectional Glenn anastomosis.

Patients and methods

Patients. Thirteen patients (5 girls and 8 boys) with single-ventricle physiology were included in this study. The mean age was 5.6 ± 1.6 years (1.5 to 17 years) and the mean body weight was 20.7 ± 4.3 kg (9.5 to 52 kg). The demographic data, diagnoses, and preoperative hemodynamic parameters determined by catheterization are summarized in Table I.

Operation and intensive care. Four patients (patients 1 through 4) underwent bidirectional cavopulmonary Glenn anastomosis[15] and nine patients (patients 5 through 13) total cavopulmonary connection according to the technique of de Leval and colleagues.[21] In seven patients undergoing total cavopulmonary connection a fenestration of the interatrial baffle[22] with a diameter of 3 or 4 mm was created because of the presence of more than two risk factors.[12] Mean aortic crossclamp time and mean time of cardiopulmonary bypass were 41 ± 5 minutes (24 to 78 minutes) and 118 ± 11 minutes (57 to 188 minutes), respectively.

Surgical repair and anesthetic management, as well as postoperative intensive therapy, were unchanged from normal practice for the study. In all patients one arterial line for continuous blood pressure monitoring and intermittent blood gas measurements and two central venous lines were placed, one in the superior caval vein for central venous pressure (CVP) recording and one in the inferior caval vein for fluid and drug administration. Additionally a 2F catheter was inserted into the left atrium for pressure tracings. After operation CVP, left atrial pressure (LAP), systemic arterial pressure, systemic arterial saturation by pulse oximetry, the electrocardiogram, and the partial pressure of end-tidal carbon dioxide ($PetCO_2$) were continuously recorded on a multichannel monitor (SMU 612, Hellige Corp., Freiburg, Germany). Dopamine (4 to 6 μg/kg per minute) and dobutamine (6 to 10 μg/kg per minute) or epinephrine (0.05 to 0.25 μg/kg per minute) were used as inotropic agents, and in cases of severely impaired systemic ventricular function milrinone (0.4 to 0.7 μg/kg per minute) was added. Continuous infusions of fentanyl (0.015 μg/kg per minute), midazolam (0.25 mg/kg per hour), and vecuronium (0.1 mg/kg per hour) were administered for sedation, analgesia, and relaxation, respectively. All patients were nasotracheally intubated and the lungs ventilated with pressure-controlled mechanical ventilators (Veolar, Hamilton Medical Inc., Rhäzuns, Switzerland, and Babylog 8000, Dräger Company, Lübeck, Germany) to achieve arterial carbon dioxide pressure levels between 35 and 40 mm Hg and pH values greater than 7.35. Daily chest x-ray films were taken to assess lung perfusion and inflation and signs of pulmonary parenchymal disease and pleural effusions.

NO administration. NO gas was obtained in a mixture with nitrogen at 450 ppm NO (Pulmonix forte, Messer Griesheim, Austria). NO was administered with use of a microprocessor-controlled system that allows NO delivery at concentrations from 1 to 40 ppm and continuous inspiratory measurements of NO and its toxic oxidative product nitrogen dioxide (NO_2) by the chemoluminescence method (Pulmonox system, Messer Griesheim, Austria). A flow box incorporated into the inspiratory limb of the ventilatory circuit transfers the inspiratory flow rate of the ventilator to the Pulmonox system, which adapts the dosage on a continuous basis. NO was administered into the inspiratory limb of the ventilatory circuit 20 cm

Table I. *Demographic and preoperative data*

Subjects	*Age (yr)*	*Weight (kg)*	*Major diagnoses*	*PAP/m (mm Hg)*	*PVRI ($U \cdot m^2$)*	*RAP (mm Hg)*	*Sao_2 (%)*
Glenn anastomosis (n = 4)							
1	1.5	11.3	PA, VSD, hypopl. LV	8	0.7	5	85
2	1.5	11	TGA, VSD, hypopl. RV	8	2.5	3	72
3	2	9.5	DILV, PA	16	1.8	6	80
4	1.8	12.5	TA	9	2.4	5	80
TCPC (n = 9)							
5	2	10.5	TA, VSD	15	1.4	8	77
6	2.7	12.5	VSD, hypopl. RV	16	1	9	84
7	15	46	TA, PA	9	2	3	82
8	1.7	9.5	Criss-cross heart, PA	12	0.5	8	80
9	3.5	12.5	DILV, PA	9	1.5	5	82
10	7	28	DORV, MA	11	1.8	8	76
11	3.4	14.2	DORV, VSD, hypopl. LV	12	1.8	6	88
12	14	52	DORV, TGA, SA, single AV valve	12	1.4	8	85
13	17	40	DORV, MA	12	2	12	70

PAP/m, Mean pulmonary artery pressure; *PVRI,* pulmonary vascular resistance index; *RAP,* right atrial pressure; *PA,* pulmonary atresia; *VSD,* ventricular septal defect; *hypopl. LV,* hypoplastic left ventricle; *TGA,* transposition of the great arteries; *hypopl. RV,* hypoplastic right ventricle; *DILV,* double-inlet left ventricle; *TA,* tricuspid atresia; *TCPC,* total cavopulmonary connection; *DORV,* double-outlet right ventricle; *MA,* mitral atresia; *SA,* single atrium.

Table II. *Hemodynamic parameters, oxygen saturation and end-tidal carbon dioxide values in nine patients with total cavopulmonary connection after exposure to inhaled NO compared with baseline*

	NO I	*p Value**	*NO 0*	*p Value†*	*NO II*
CVP (mm Hg)	17.6 ± 1 (14-22)	0.0001	21 ± 1.1 (16-26)	0.0001	17.8 ± 1 (14-22)
LAP (mm Hg)	9.7 ± 0.9 (6-14)	0.0006	7.6 ± 1.1 (3-14)	0.0011	9.2 ± 1.1 (5-16)
TPG (mm Hg)	7.9 ± 0.6 (6-12)	0.0001	13.5 ± 0.8 (10-18)	0.0013	7.7 ± 1 (4-12)
SAP (mm Hg)	64 ± 3 (56-82)	0.031	59 ± 4 (43-79)	0.0054	65 ± 4 (54-86)
HR (beats/min)	130 ± 7 (98-155)		131 ± 7 (97-153)		130 ± 7 (97-152)
Sao_2 (%)	94 ± 1 (88-98)	0.0004	86 ± 1 (82-93)	0.0004	94 ± 1 (88-98)
Svo_2 (%)	71 ± 3 (61-78)	0.037	63 ± 3 (58-72)	0.023	72 ± 2 (65-78)
$Petco_2$ (mm Hg)	32 ± 1.3 (26-39)	0.0005	29 ± 1.6 (22-37)	0.0005	32 ± 1.3 (25-39)

Data are expressed as mean values plus or minus the standard error of the mean (range).

NO I, NO II, Exposure to NO; *NO 0,* baseline; *TPG,* transpulmonary pressure gradient (CVP − LAP); *SAP,* mean systemic arterial pressure; *HR,* heart rate; *Svo_2,* mixed venous blood oxygen saturation.

*NO 0 vs NO I.

†NO 0 vs NO II.

proximal to the endotracheal tube with use of an airway sampling adapter (Engström sampling adapter, Gambrö Engström, Bromma, Sweden). The system was calibrated before each treatment and measurement with special calibration gases. Methemoglobin was measured 2 hours after the start of NO therapy and then two to three times daily (CO-Oxylite AVL 912, AVL Corp., Graz, Austria).

Study protocol. Indication for treatment with NO was a transpulmonary pressure gradient (CVP − LAP) of more than 10 mm Hg or a CVP more than 20 mm Hg in the early postoperative period after exclusion of relevant atrioventricular valve insufficiency, severe impairment of systemic ventricular function, and pulmonary venous or arterial obstruction by two-dimensional transthoracic or transesophageal echocardiography. NO was delivered at the lowest effective dose to obtain a transpulmonary pressure gradient less than 10 mm Hg or a decrease in the transpulmonary pressure gradient of more than 20%. After 12 to 18 hours of stable hemodynamics the first NO switch on/off trial was done. Inhaled NO administration was discontinued for 5 minutes to perform a baseline study, followed by a continuation of NO treatment at the same dose as used in the initial period. Ventilation parameters (mean airway pressure, mean 9 ± 0.5 cm H_2O, range 7 to 14 cm H_2O) and fractional inspired oxygen concentration (mean 0.8 ± 6, range 0.4 to 1.0) and inotropic support remained unchanged during the study period. A complete set of measurements was recorded 5 minutes after the beginning of each period including heart rate, mean systemic arterial pressure, CVP, LAP, arterial oxygen saturation (Sao_2), venous oxygen saturation, and $Petco_2$.

Weaning of the patient from inhaled NO therapy was attempted every day by decreasing NO concentration by 50% and finally discontinuing NO administration when

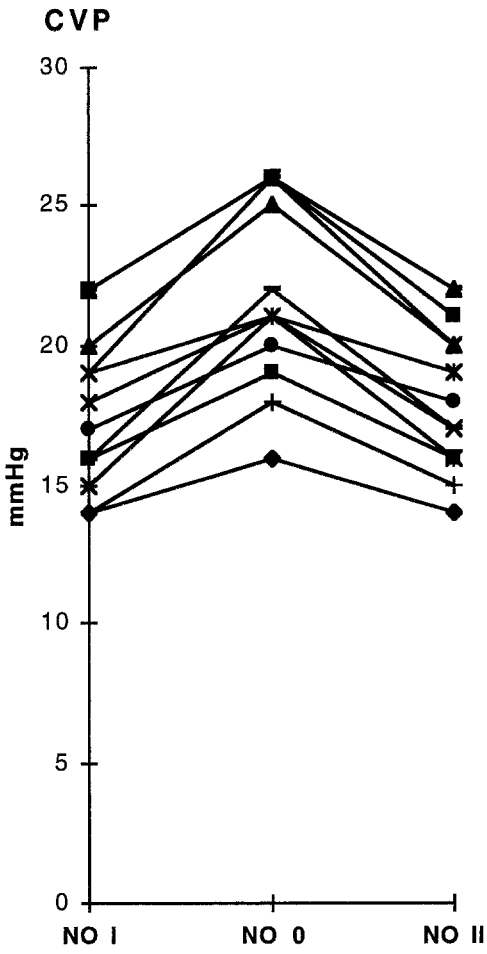

Fig. 1. CVP after exposure to inhaled NO *(NO I, NO II)* compared with baseline value *(NO 0)*.

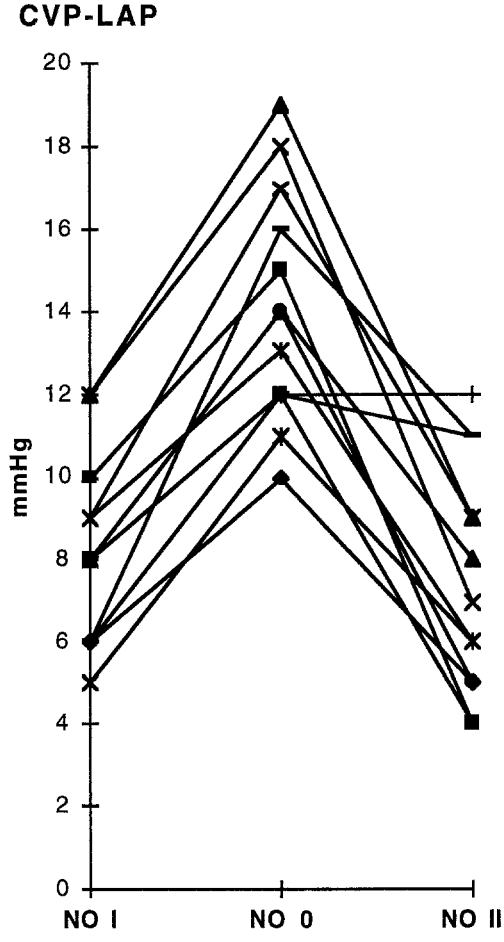

Fig. 2. Transpulmonary pressure gradient (CVP − LAP) after exposure to inhaled NO *(NO I, NO II)* compared with baseline value *(NO 0)*.

the inhaled NO dose was only 1 ppm. If weaning from inhaled NO resulted in worsening of the cardiorespiratory state, the patients were first weaned from ventilatory support; after successful extubation NO was administered by means of nasal prongs. The study protocol was approved by the local ethics committee. Informed consent concerning the nature of the study was obtained from the parents of all patients.

Statistical analysis. All data are expressed as mean ± standard error of the mean (range) and as mean percentage change ± standard error of the mean. The effects of NO on hemodynamic parameters and oxygenation were compared with baseline findings by means of the two-tailed paired Student's t test. A p value < 0.05 was considered statistically significant.

Results

Before the start of NO inhalation therapy, mean CVP and mean transpulmonary pressure gradient were 22 ± 0.9 mm Hg (16 to 25 mm Hg) and 14.2 ± 0.7 mm Hg (11 to 19 mm Hg), respectively.

In the patient group undergoing total cavopulmonary connection ($n = 9$) inhaled NO therapy significantly decreased CVP by 15.3% ± 1.4% ($p = 0.0001$) and the transpulmonary pressure gradient (CVP − LAP) by 42% ± 8% ($p = 0.0008$). LAP and mean systemic arterial pressure values increased by 28% ± 8% ($p = 0.007$) and 12% ± 3.6% ($p = 0.011$), respectively. Heart rate remained unchanged during the study period. Inhaled NO improved Sao_2 values by 8.2% ± 1% ($p = 0.005$) and venous oxygen saturation values by 14% ± 4% ($p = 0.03$), whereas $Petco_2$ values increased by 12% ± 3% ($p = 0.002$) (Table II, Figs. 1 through 4).

In four patients with bidirectional Glenn anastomosis (Table III) NO inhalation therapy resulted in

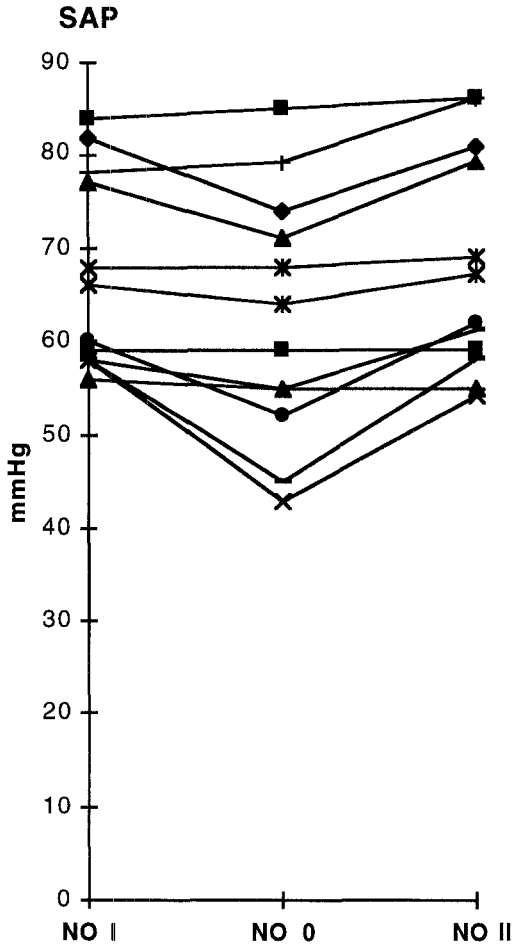

Fig. 3. Mean systemic arterial pressure *(SAP)* after exposure to inhaled NO *(NO I, NO II)* compared with baseline values *(NO 0)*.

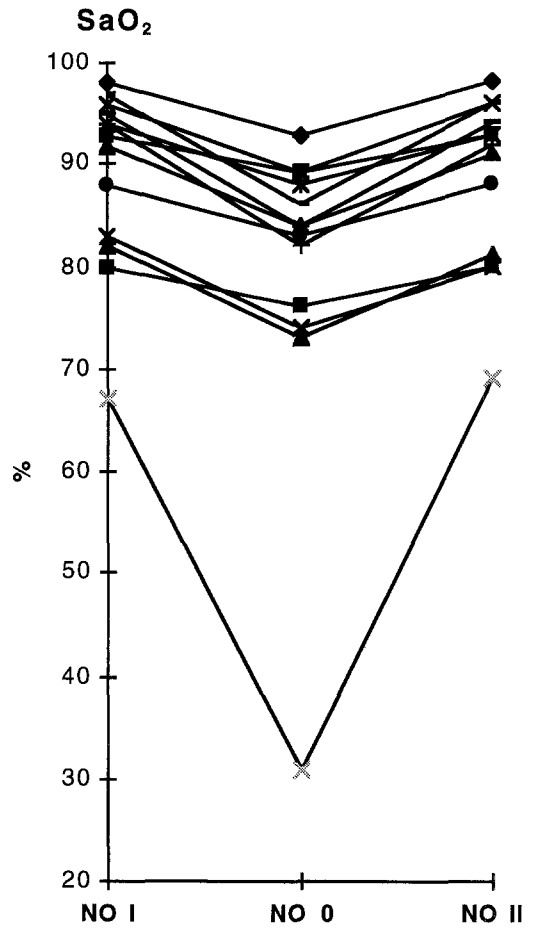

Fig. 4. Sao_2 after exposure to inhaled NO *(NO I, NO II)* compared with baseline values *(NO 0)*.

a decrease of CVP and of the transpulmonary pressure gradient by 22% ± 1% and 55% ± 6%, respectively. After NO exposure values of LAP and mean systemic arterial pressure increased by 13% ± 7% and 5.5% ± 2%, respectively. Inhalation of NO improved Sao_2 values by 37% ± 29% and venous oxygen saturation values by 11% ± 3%, whereas $Petco_2$ values increased by 12% ± 6% (Figs. 1 through 4). In a 1.8-year-old patient with tricuspid atresia (patient 4) the most significant improvement of Sao_2 values from 31% to 69% was observed, whereas CVP decreased from 21 to 15 mm Hg.

Patients were treated with inhaled NO for 106 ± 19 hours, ranging from 12 to 264 hours. Mean NO concentration was 4.1 ± 0.7 ppm, ranging from 1.5 to 10 ppm. Methemoglobin levels measured 3 to 4 times daily in each patient ranged from 0.6% to 2.3% (mean 1.2% ± 0.16%) and NO_2 concentrations never exceeded 0.1 ppm. No other side effects were observed. In three patients NO inhalation therapy was continued by means of nasal prongs for 0.5 to 48 hours after extubation. The mean duration of mechanical ventilation was 6.0 ± 1.0 days (1.5 to 18 days). In one patient, who required artificial ventilation for 18 days, the postoperative course was complicated by septicemia associated with multiorgan failure. One patient died of cerebral hemorrhage 5 days after weaning from NO inhalation with a stable hemodynamic condition on postoperative day 10.

Discussion

Postoperative morbidity and mortality after Fontan-type operations are mainly related to low cardiac output associated with high CVP values as a

Table III. *Hemodynamic parameters, oxygen saturation and end tidal carbon dioxide values in four patients with bidirectional Glenn anastomosis after exposure to inhaled NO compared with baseline*

	NO I	*NO 0*	*NO II*
CVP (mm Hg)	19 ± 1.5 (15-22)	24.5 ± 1.2 (21-26)	19.3 ± 1.1 (16-21)
LAP (mm Hg)	10 ± 0.8 (8-12)	9 ± 1.1 (6-11)	10 ± 0.8 (8-12)
TPG (mm Hg)	9 ± 1.5 (5-12)	15.5 ± 1.7 (11-19)	7 ± 1.2 (4-9)
SAP (mm Hg)	73 ± 4 (66-84)	71 ± 5 (64-85)	75 ± 5 (67-86)
HR (beats/min)	143 ± 6 (132-154)	143 ± 6 (131-155)	143 ± 6 (131-155)
Sao_2 (%)	78 ± 4 (67-83)	64 ± 11 (31-76)	78 ± 3 (69-81)
Svo_2 (%)	66 ± 5 (56-75)	59 ± 6 (47-68)	66 ± 6 (55-75)
$Petco_2$ (mm Hg)	27 ± 2.4 (20-30)	24.3 ± 3 (16-29)	27 ± 2 (20-30)

Data are expressed as mean values plus or minus the standard error of mean (range).

NO I and NO II, Exposures to NO; *NO 0,* baseline; *TPG,* transpulmonary pressure gradient (CVP − LAP); *SAP,* mean systemic arterial pressure; *HR,* heart rate; *Svo_2,* mixed venous blood oxygen saturation.

result of elevated PVR, hypoplastic or distorted pulmonary arteries, or systemic ventricular dysfunction.[12-14, 16] In the early postoperative period PVR is most labile because of pulmonary endothelial dysfunction after cardiopulmonary bypass.[23] Thus even minor elevations of PVR may result in a severe impairment of pulmonary perfusion and consequently in low cardiac output syndrome.[16] Aggressive mechanical ventilation may further decrease pulmonary perfusion.[24] Various intravenous vasodilators have been used to reduce elevated PVR values after cardiac operations, but all these agents also decrease systemic vascular resistance and may increase ventilation-perfusion mismatch in the presence of additional parenchymal lung disease.[25, 26] In contrast, inhaled NO acts only locally in the adjacent pulmonary smooth muscle cell producing selective pulmonary vasodilation and is rapidly inactivated by binding to hemoglobin in the circulation, which precludes systemic vasoactive effects.[27, 28]

In this study therapy with inhaled NO significantly improved hemodynamic conditions and arterial and venous oxygenation in patients with critical pulmonary perfusion in the early postoperative period after Fontan-type procedures and bidirectional Glenn anastomosis. In the patient group undergoing total cavopulmonary connection inhaled NO therapy decreased significantly elevated CVP and transpulmonary pressure gradients between CVP and LAP, whereas LAP increased. Although pulmonary blood flow was not measured, these hemodynamic changes together with the rise of levels of Sao_2 and of $Petco_2$ indicate an improvement of pulmonary perfusion by selective lowering of postoperatively elevated PVR. Consequently the increase of pulmonary blood flow resulted in improved filling of the systemic ventricle associated with a significant rise of mean systemic arterial pressure, which may indicate together with the increase in venous oxygen saturation an improvement of cardiac output. However, the arteriovenous oxygen saturation difference, which might be the best indicator of cardiac output in this circumstance, did not change in our patients during NO inhalation therapy.

In patients with fenestrated total cavopulmonary connection the reduction of the interatrial right-to-left shunt as a result of the decrease in CVP might have also contributed to the increase of Sao_2. Similar observations of improvement of hemodynamics and oxygenation in two patients after Fontan repair have been described by Miller, James, and Elliot[17] and Yahagi and associates.[18]

We also observed in our patients with bidirectional Glenn anastomosis a decrease in CVP and of transpulmonary pressure gradient and simultaneously an increase in Sao_2 after NO inhalation therapy, indicating an improvement of pulmonary perfusion. LAP and systemic arterial pressure values remained nearly unchanged. Because in the Glenn circulation inferior vena caval blood reenters the systemic circulation directly without passing the lungs, an improvement of pulmonary perfusion by inhaled NO therapy may only partially influence LAP and systemic ventricular preload, and consequently systemic arterial pressure. In contrast to our results Adatia and colleagues[20] reported no beneficial effect of inhaled NO on transpulmonary pressure gradients and Sao_2 values in six patients after bidirectional Glenn anastomosis and suggested that PVR was not elevated in their patients. This explanation seems likely because the mean CVP value and transpulmonary pressure gradient in their patients were 17 mm Hg and 8 mm Hg, respectively,

compared with a mean CVP value of 24.5 mm Hg and a mean transpulmonary pressure gradient of 15.5 mm Hg in our patients.

The systemic oxygen desaturation in our patients was mainly caused by the residual right-to-left shunt at the atrial level inasmuch as chest x-ray films and clinical observations excluded significant pulmonary parenchymal diseases. Because a postoperative ventilation-perfusion mismatch cannot be excluded in all our patients the improved oxygenation might be also related to an improvement of ventilation-perfusion relationship by NO.

We used a low-dose NO regimen between 1.5 and 10 ppm; however, we did not perform dose-response testing. The effectiveness of low doses of inhaled NO for the treatment of adult respiratory distress syndrome,[29] persistent pulmonary hypertension in neonates,[6] and pulmonary hypertension after cardiac operations in children[9] has been reported previously. In our study the doses of inhaled NO between 1.5 and 10 ppm were below recommended safety guidelines.[30] Methemoglobin levels measured several times daily and NO_2 concentrations never reached clinically important values. The use of low doses of inhaled NO and a short duration of NO treatment reduce the risk of toxicity. Although we observed uniform hemodynamic reactions in all our patients after the start of NO therapy, our study may reflect the effects of withdrawal of NO rather than the hemodynamic effect of initiation of NO. One possible limitation of our study, however, is a known withdrawal phenomenon that transiently raises PVR even after a short exposure period of low-dose NO therapy. On the basis of our study design we certainly cannot exclude this in our patients.

In conclusion, this study demonstrates that inhaled NO even in low doses between 1.5 and 10 ppm improves critical pulmonary perfusion and oxygenation in the early postoperative period after Fontan-type procedures and bidirectional Glenn anastomosis. We suggest that this treatment might play an important role in the management of transient critical pulmonary perfusion caused by reactive elevated PVR levels after Fontan-type operations and bidirectional Glenn anastomosis. Nevertheless, further studies are required to show the impact of this new treatment on postoperative morbidity and clinical outcome of these operations.

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