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Nitric Oxide in the Evaluation of Congenital Heart Disease with Pulmonary Hypertension: Factors Related to Nitric Oxide Response

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Abstract. Inhaled nitric oxide (NO) has been used in the preoperative evaluation of patients with congenital heart disease and pulmonary hypertension. The purpose of this study was to characterize responses in pulmonary vascular resistance (PVR) to oxygen and increasing doses of NO during cardiac catheterization and to determine if any related factors affect the response of the pulmonary vascular bed to NO. A prospective analysis of 42 patients (median age, 3.0 years) with congenital heart disease and pulmonary hypertension who underwent NO testing was performed. Systemic vascular resistance (SVR) and PVR were assessed in room air, 100% oxygen, and oxygen plus 20, 40, and 80 parts per million (ppm) NO. Changes in pulmonary artery pressure, PVR, and SVR were assessed. The response to NO was then correlated to individual patient's age, gender, type of heart defect, the presence of trisomy 21, and baseline PVR/SVR. There was a greater decrease in PVR and PVR/SVR with 20 ppm NO than with oxygen alone. There was no additional decrease at 40 or 80 ppm NO. There was no correlation between age, gender, type of congenital heart disease, and baseline PVR/SVR ratio with the degree of response to NO. Patients with trisomy 21 had less of a response to NO ($p = 0.017$) than patients without trisomy 21. There is no difference in determining PVR response with doses of NO beyond 20 ppm during cardiac catheterization. Age, gender, and baseline PVR/SVR ratio are not associated with responsiveness to NO. Patients with trisomy 21 may be less responsive to NO.

Key words: Pulmonary hypertension — Congenital heart defects — Nitric Oxide — Cardiac catheterization

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Inhaled nitric oxide (NO) has been shown to decrease pulmonary vascular resistance (PVR) in patients with congenital heart disease (CHD) and pulmonary hypertension [10]. Postoperatively, it has been used to treat or prevent pulmonary hypertensive crises and improve oxygen saturations and cardiac output, which may be adversely affected by elevated pulmonary artery pressures [6, 9]. Inhaled NO has also been used in the preoperative evaluation of patients with CHD and pulmonary hypertension to determine the reactivity of the pulmonary vascular bed [1]. Typically, this has been done using increasing concentrations of NO. There are few studies in the pediatric population that assess the utility of preoperative testing with different concentrations of NO on PVR. In addition, there are few studies assessing the effect of demographic and patient factors to the response to NO. The purposes of this study were to characterize the responses of PVR to oxygen and NO in patients with CHD undergoing cardiac catheterization, to determine changes in PVR to oxygen as well as increasing concentrations of NO, and to determine if there were any factors related to the degree of response to NO.

Materials and Methods

The study population consisted of 42 patients with CHD and elevated PVR who underwent oxygen and inhaled NO testing during cardiac catheterization at our institution from March 1997 to January 2001. Elevated PVR was defined as PVR systemic vascular resistance (SVR) $=0.25$, with an initial PVR of at least 5 Wood units. Only patients with elevated PVR and CHD or cardiomyopathy were included. Patients with primary pulmonary hypertension were excluded from the study. Prior to catheterization, written informed consent was obtained from each patient or legal guardian. An institutional review board for human research approved the protocol for this study.

Variables evaluated included pulmonary artery pressures, systemic arterial pressures, and pulmonary and systemic blood flows measured using the Fick equation. Variables for the Fick

equation were determined using assumed and constant oxygen consumptions. Measured oxygen saturations in the superior vena cava, pulmonary artery, pulmonary vein, and femoral artery and pulmonary vein blood gasses were used when the patient was receiving oxygen. From these data, PVR, SVR, and PVR/SVR were calculated. Measurements for PVR and SVR were indexed to body surface area. All values were calculated in room air as a baseline, 100% oxygen, and 100% oxygen plus 20, 40, and 80 parts per million (ppm) of NO. Patients remained at each condition for a period of 10 minutes before pressures and oxygen saturations were measured. Patients were not returned to baseline room air conditions between changes. A paired student *t*-test was used to compare the changes in values of PVR and PVR/SVR at differing levels of NO. The Pearson correlation was used to determine if there was a relationship of responsiveness to NO and age, gender the presence of trisomy 21, or other variables. A regression model was used to calculate an r^2 value where applicable. A p value of less than 0.05 was considered significant.

Results

There were 42 patients enrolled in the study (22 males and 20 females). Median patient age was 3.0 years, with a range of 2 months to 27 years. The cardiac diagnoses of the patients are listed in Table 1. There were 11 patients (26%) with trisomy 21 [7] complete atrioventricular (AV) canal, 2 ventricular septal defect, 1 atrial and ventricular septal defect, and 1 tetralogy of Fallot with complete AV canal]. Patients with trisomy 21 were younger at catheterization than those without chromosomal defects (average age, 2.9 ± 4.1 vs 4.5 ± 8.2 years). Four patients had undergone previous surgery: 1 tetralogy of Fallot patient who had a Waterston-Cooley shunt in infancy, 1 tetralogy of Fallot patient who had a full repair at 4 years of age, 1 heterotaxy syndrome patient with complex CHD who had a pulmonary band, and 1 patient with atrial and ventricular septal defects who had significant ventricular-level shunting after repair in infancy. In 40 patients (95%), testing was performed following endotracheal tube intubation. In the remaining 2 patients, testing was performed while breathing spontaneously.

Mean PVR was 12.2 ± 8.2 Wood units with a mean PVR/SVR of 0.53 ± 0.25. The mean initial pulmonary blood flow-to-systemic blood flow ratio was 1.6 ± 0.8. A total of 33 of 42 (79%) patients responded to oxygen or oxygen plus inhaled NO. There were 30 patients who responded to both oxygen alone and oxygen plus NO. An additional 3 patients responded to oxygen and NO in combination but not to oxygen alone. The mean PVR decreased to 9.9 ± 7.9 Wood units ($p < 0.02$ compared to baseline) on 100% oxygen (Fig. 1). The PVR further decreased to 8.4 ± 7.6 Wood units ($p < 0.01$ compared to baseline and $p < 0.04$ compared to oxygen alone) when 20 ppm of NO was given to the patients on 100% oxygen. There was no further decrease in the PVR with an increase to 40 or 80 ppm of NO. The mean PVR was 8.3 ± 7.4 Wood units on 40 ppm of NO and 8.2 ± 7.2 Wood units on 80 ppm of NO. Table 2 lists the responses of PVR, SVR, PVR/SVR, systolic and diastolic pulmonary artery pressure, mean pulmonary artery pressure, and pulmonary capillary wedge pressure to oxygen and NO.

Table 1. Cardiac Diagnoses

Diagnosis	No. of patients
Ventricular septal defect with or without atrial septal defect	16
Complete atrioventricular canal defect	11
Cardiomyopathy (dilated or restrictive)	6
Mitral atresia with coarctation	3
Tetralogy of Fallot	2
Aortic stenosis	2
Tricuspid atresia	2

The PVR/SVR (Fig. 2) decreased an average of 27% from baseline with the addition of 100% oxygen alone ($p < 0.01$ compared to baseline). The PVR/SVR decreased an average of 38% when compared to baseline ($p < 0.01$) with the addition of 20 ppm of NO, and there was a decrease of 11% when compared to patients on 100% oxygen alone ($p < 0.02$). The changes in PVR at baseline compared to 20 ppm NO are shown in Fig. 3. There was no further decrease in PVR/SVR with increasing concentrations of inhaled NO to 40 and 80 ppm. There were no significant differences in the response to NO relative to age, gender, type of CHD, baseline PVR, and baseline PVR/SVR. However, there was a difference in responses in patients with trisomy 21. In patients without chromosomal abnormalities, there was an average of a 42% decrease in PVR with the addition of NO. In patients with trisomy 21, there was only a 21% decrease. When correcting for age, baseline PVR, and type of CHD, this difference is significant ($p = 0.02$). Using a regression model, approximately 12% of the variation in PVR can be explained by the presence of trisomy 21 (r^2 12.2%, $p < 0.017$).

Discussion

In recent years, NO has been used in both therapeutic and diagnostic trials in patients with CHD in both the preoperative and postoperative periods [3, 11]. In this study, we evaluated the preoperative use of NO in the cardiac catheterization laboratory to determine pulmonary vascular reactivity. In a study by Azeka and colleagues [2], inhaled NO had a greater effect in decreasing the PVR than oxygen alone in the cardiac catheterization laboratory. Our study also showed a significant decrease in the PVR with the addition of

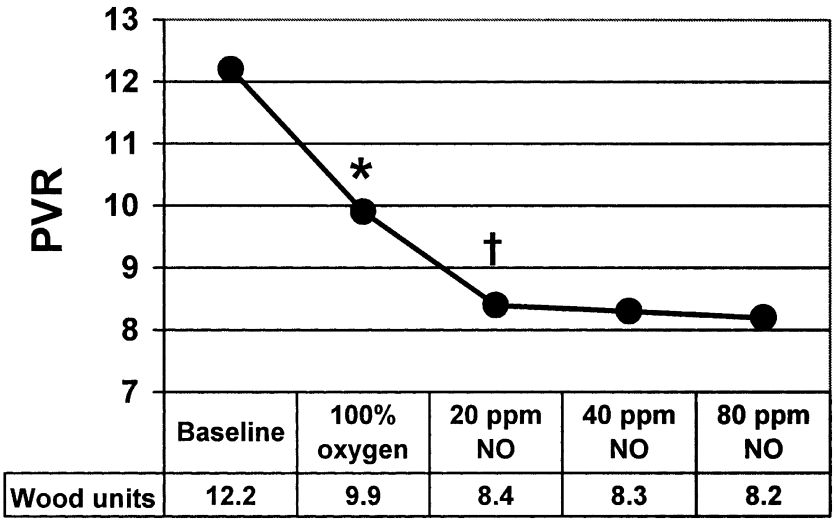

Fig. 1. Decrease in pulmonary vascular resistance (*PVR*) with 100% oxygen and 100% oxygen plus 20, 40, and 80 ppm of nitric oxide (*NO*). There was a significant decrease ($p < 0.02$) in PVR with the addition of 100% oxygen (*). There was also a significant decrease with the addition of 20 ppm NO (+): $p < 0.01$ compared to baseline and $p < 0.04$ compared to 100% oxygen alone.

Table 2. Responses of variables to oxygen and nitric oxide

	PVR	SVR	PVR/SVR	PA pressure[a]	PA mean pressure[a]	Wedge pressure[a]
Room air	12.2 ± 8.2	23.0 ± 8.5	0.53 ± 0.25	79/36	54 ± 18	15 ± 7
100% oxygen	9.9 ± 7.9	25.8 ± 8.6	0.38 ± 0.26	70/33	49 ± 20	16 ± 7
20 ppm NO + 100% O_2	8.4 ± 7.6	26.9 ± 9.1	0.31 ± 0.22	67/32	46 ± 19	16 ± 8
40 ppm NO + 100% O_2	8.3 ± 7.4	26.2 ± 9.6	0.32 ± 0.23	66/31	46 ± 20	16 ± 9
80 ppm NO + 100% O_2	8.2 ± 7.2	25.2 ± 9.2	0.33 ± 0.27	67/32	46 ± 20	17 ± 10

NO, nitric oxide; O_2, oxygen; PA, pulmonary artery; ppm, parts per million; *PVR*, pulmonary vascular resistance; *PVR/SVR*, pulmonary vascular-to-systemic vascular resistance ratio; *SVR*, systemic vascular resistance.
[a]All pressures in millimeters of mercury.

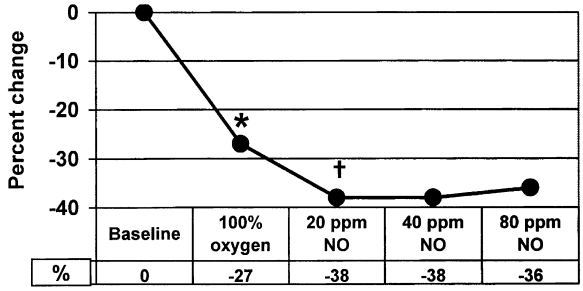

Fig. 2. Percentage decrease of pulmonary vascular resistance (*PVR*) to systemic vascular resistance (*SVR*) ratio with 100% oxygen and 100% oxygen plus 20, 40, and 80 ppm of nitric oxide (*NO*). There was a significant decrease ($p < 0.01$) in PVR/SVR with the addition of 100% oxygen (*). There was also a significant decrease with the addition of 20 ppm NO (+): $p < 0.01$ compared to baseline and $p < 0.02$ compared to 100% oxygen alone.

NO to patients on 100% inspired oxygen. In addition, our study showed a significant decrease in the PVR/SVR with the addition of NO.

The presence of a direct dose-response relationship for NO has been a topic of debate. The pulmonary vasodilatory effects of NO have been demonstrated in concentrations as low as 0.8 ppm [4]. Several studies have demonstrated a plateau effect for NO during short-term usage. Finner et al. [8] demonstrated no significant difference in systemic oxygenation between 5 and 80 ppm of NO in newborns with persistent pulmonary hypertension. Day and colleagues, [7] found that PVR was selectively decreased to a similar extent by 12 and 60 ppm inhaled NO in 11 patients with a ventricular septal defect and pulmonary hypertension. Miller et al. [9] showed no dose response among 2, 10, and 20 ppm NO in 10 infants with pulmonary hypertension following surgical correction of their congenital heart defect. Our study supports the theory of a plateau effect rather than an incremental effect for NO with short-term usage.

In many institutions, preoperative NO testing has been performed using 20, 40, and 80 ppm of NO, allowing the patient 10 minutes on each concentration to equilibrate [10]. Our study suggests that testing at multiple concentrations higher than 20 ppm is not necessary. No additional information is gained by testing PVR and PVR/SVR at multiple concentrations versus a single concentration. Because these patients are at a high risk for adverse reactions during catheterization, the decrease in the amount of time

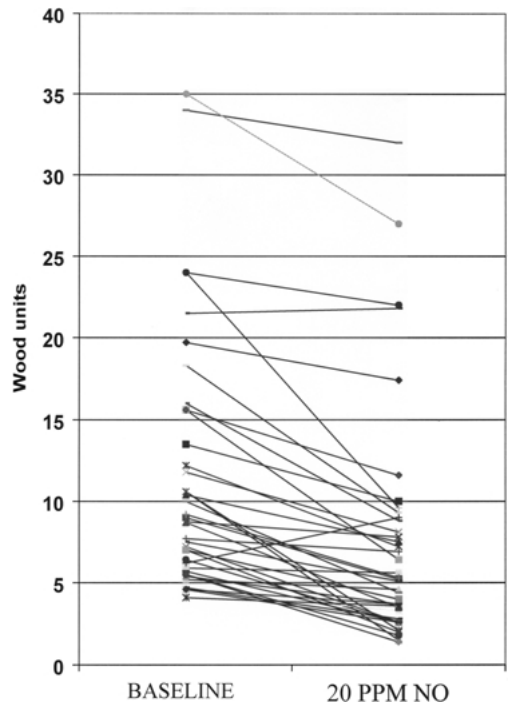

Fig. 3. Plot of change in pulmonary vascular resistance at baseline compared to 20 ppm in all patients studied.

required in the cardiac catheterization laboratory for the procedure and sedation/anesthesia has potential benefits and does not compromise the quality of the data obtained.

Patients with trisomy 21 have abnormal pulmonary vasculature and are at a higher risk for developing pulmonary hypertension. This study suggests that this patient population also does not respond as well to NO as those patients without chromosomal abnormalities. Although patients with trisomy 21 respond to NO, the effect on the pulmonary vasculature is diminished. This may have important clinical ramifications in patients with trisomy 21 and pulmonary hypertension who undergo surgery. Long-term studies need to be performed to determine if this diminished response to NO is clinically significant. In this study, only 1 of the 11 patients was considered inoperable on the basis of the elevated pulmonary vascular resistance in the catheterization laboratory. However, all patients with trisomy 21 were placed on NO in the postoperative period, and 1 patient with trisomy 21 died in the postoperative period, with pulmonary hypertension playing a significant role.

Although data regarding a decrease in PVR and PVR/SVR can be obtained using a single concentration of NO, it is yet to be determined what degree of decrease in PVR or PVR/SVR using NO makes a person an acceptable candidate for surgery. Further studies need to be performed to determine what level of preoperative PVR and PVR/SVR response increases surgical morbidity and mortality.

This study has several limitations. The patient population was heterogeneous with a broad distribution of cardiac diagnoses. Some studies report that approximately half of pediatric patients with CHD pulmonary hypertension have trisomy 21 [5]. In this study, only 26% of the patients had trisomy 21. Dose-dependent effects over more prolonged periods and at NO concentrations less than 20 ppm were not evaluated in this study and thus cannot be excluded. Another significant limitation is the fact that the PVR and SVR were calculated using assumed (rather than measured) oxygen consumptions, and therefore the effect of NO on oxygen consumptions was not evaluated. The majority of patients in this study were intubated for the procedure, and it is difficult to obtain accurate oxygen consumptions for patients who are intubated. Patients were intubated to attempt to minimize the effects of hyperventilation or hypercarbia on the PVR. It is standard at our institution to use assumed rather than measured oxygen consumptions. However, measured oxygen consumptions could give a more accurate reflection of the effects of NO on the pulmonary vascular bed. Patient data were collected 10 minutes after patients were placed on NO or after the NO dose was increased. There are few data regarding the optimal timing for data collection after a patient has been placed on NO, and 10 minutes may not be the optimal amount of time to see maximal hemodynamic effects. Another possible limitation is that most patients in this study were intubated. Although mechanical ventilation may control for hypoventilation that may affect PVR, it does not represent the normal physiologic mechanism of respiration, However, it does control for varying levels of carbon dioxide that influence PVR. In addition, there is also the potential for a type II error in the statistical analysis given the relatively small size of the patient population.

Conclusions

There is no difference in PVR response with doses of inhaled NO greater than 20 ppm in the cardiac catheterization laboratory. Age, gender, type of congenital heart defect, baseline PVR, and PVR/SVR are not associated with response to inhaled NO. Patients with trisomy 21 may be less responsive to NO.

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