Journal of the American College of Cardiology
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Published by Elsevier Science Inc.

Vol. 33, No. 3, 1999
ISSN 0735-1097/99/$20.00
PII S0735-1097(98)00668-8

Combined Effects of Nitric Oxide and Oxygen During Acute Pulmonary Vasodilator Testing

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OBJECTIVES We compared the ability of inhaled nitric oxide (NO), oxygen (O_2) and nitric oxide in oxygen ($NO+O_2$) to identify reactive pulmonary vasculature in pulmonary hypertensive patients during acute vasodilator testing at cardiac catheterization.

BACKGROUND In patients with pulmonary hypertension, decisions regarding suitability for corrective surgery, transplantation and assessment of long-term prognosis are based on results obtained during acute pulmonary vasodilator testing.

METHODS In group 1, 46 patients had hemodynamic measurements in room air (RA), 100% O_2, return to RA and NO (80 parts per million [ppm] in RA). In group 2, 25 additional patients were studied in RA, 100% O_2 and 80 ppm NO in oxygen ($NO+O_2$).

RESULTS In group 1, O_2 decreased pulmonary vascular resistance (PVR) (mean ± SEM) from 17.2 ± 2.1 U·m^2 to 11.1 ± 1.5 U·m^2 ($p < 0.05$). Nitric oxide caused a comparable decrease from 17.8 ± 2.2 U·m^2 to 11.7 ± 1.7 U·m^2 ($p < 0.05$). In group 2, PVR decreased from 20.1 ± 2.6 U·m^2 to 14.3 ± 1.9 U·m^2 in O_2 ($p < 0.05$) and further to 10.5 ± 1.7 U·m^2 in $NO+O_2$ ($p < 0.05$). A response of 20% or more reduction in PVR was seen in 22/25 patients with $NO+O_2$ compared with 16/25 in O_2 alone ($p = 0.01$).

CONCLUSIONS Inhaled NO and O_2 produced a similar degree of selective pulmonary vasodilation. Our data suggest that combination testing with $NO+O_2$ provides additional pulmonary vasodilation in patients with a reactive pulmonary vascular bed in a selective, safe and expeditious fashion during cardiac catheterization. The combination of $NO+O_2$ identifies patients with significant pulmonary vasoreactivity who might not be recognized if O_2 or NO were used separately. (J Am Coll Cardiol 1999;33:813–9) © 1999 by the American College of Cardiology

Elevated pulmonary vascular resistance (PVR) complicates the evaluation, clinical course and outcome of patients with congenital heart disease or end-stage pulmonary disease. It is a crucial factor in determining the timing or type of intervention, and has been invoked as the primary determinant of mortality in many lesions (1,2). Opinion varies on what resistance must be achieved with vasodilator testing to insure safe operability for children with congenital heart disease. An increased or fixed elevation in PVR may deny patients the chance of corrective surgery, leaving them susceptible to the development of progressive obliterative pulmonary vascular disease and reduced life expectancy (3,4). Demonstration of pulmonary vasoreactivity in patients with end-stage pulmonary disease may differentiate patients who would benefit from long-term medical therapy (5,6) from those with high, fixed resistance who should be more urgently considered for lung transplantation (3). Safe and expeditious demonstration of maximal pulmonary vasodilation in patients with a reactive pulmonary bed is therefore an important objective.

Many vasodilators have been utilized for diagnostic testing during cardiac catheterization. Systemic vasodilators with their attendant risks of hypotension and increased intrapulmonary shunt may be hazardous (7), especially in patients with ventricular outflow tract obstruction. Breathing oxygen (O_2) remains a standard means of pulmonary vasodilator testing in pediatric cardiac catheterization laboratories (8,9). However, failure to respond to acute treatment with O_2 has been reported in some patients who did indeed have reactive pulmonary vasculature (3,10).

Inhaled nitric oxide (NO) is a selective pulmonary vasodilator with minimal systemic effects and does not increase intrapulmonary shunting. It can be administered easily with O_2 or room air (RA) during cardiac catheterization by either ventilator or mask. The purpose of this study was to compare the ability of NO and O_2 to identify patients with a reactive pulmonary vascular bed during cardiac catheter-

From the Department of Cardiology, Children's Hospital, and the Department of Pediatrics, Harvard Medical School, Boston, Massachusetts. Dr. Atz is supported by an award from the National Institutes of Child Health and Human Development and a grant from the United States Food and Drug Administration. Dr. Wessel is supported by grants from the United States Food and Drug Administration and the Research Endowment of Children's Hospital. Presented in part at the 45th Annual Scientific Sessions of the American College of Cardiology, Orlando, Florida, March 1996.

Manuscript received April 10, 1998; revised manuscript received September 18, 1998, accepted October 30, 1998.

Abbreviations and Acronyms

FiO_2	= fraction of inspired oxygen
NO	= nitric oxide
NO_2	= nitrogen dioxide
O_2	= oxygen
$PaCO_2$	= partial pressure of carbon dioxide, arterial
PCO_2	= partial pressure of carbon dioxide
ppm	= parts per million
PVR	= pulmonary vascular resistance
RA	= room air

ization. We further compared the hemodynamic effects of breathing nitric oxide in oxygen ($NO+O_2$) to breathing O_2 alone during acute vasodilator testing.

METHODS

We enrolled patients between January 1992 and December 1996 who had mean pulmonary artery pressure ≥30 mm Hg, PVR >3 U·m^2, and were determined during catheterization to require vasodilator testing. We included for analysis 71 patients who had complete hemodynamic measurements to allow calculation of vascular resistances.

Study groups. The first 46 patients (group 1) were studied under the following four study conditions: A) in RA; B) after breathing 100% O_2 for 15 min; C) after another 15 min in RA, and D) after 15 min breathing NO at 80 parts per million (ppm) in 23% O_2 (NO+RA). As NO is titrated into a delivery circuit, the delivered fraction of inspired O_2 (FiO_2) is decreased. Therefore a small amount of supplemental O_2 (23%) was added to NO to avoid administration of a hypoxic gas mixture. The patients in group 1 had a median age of 6.5 years, range 4 months to 59 years.

Twenty-five additional patients (group 2) were studied in the following three conditions: A) in RA; B) after breathing 100% O_2 for 15 min, and C) after 15 min of inhaling 80 ppm NO in 91% O_2. This was the maximal FiO_2 attainable after dilution with 80 ppm of NO. Patients in group 2 had a median age of 3.5 years, range 5 months to 69 years.

The patients in each group represented a broad spectrum of diagnoses characteristic of a high volume pediatric cardiac catheterization laboratory. Most had unrepaired or previously palliated congenital heart disease, although some had end-stage pulmonary disease (Tables 1 and 2). Four of 46 patients in group 1 and three of 25 patients in group 2 were mechanically ventilated. The remainder in each group were breathing spontaneously. Sedation was given according to a routine, which included intravenous morphine and midazolam. Partial pressure of carbon dioxide (PCO_2) was normal throughout the study in both groups.

Hemodynamic assessment. Hemodynamic measurements included left atrial, right atrial, pulmonary and systemic arterial pressures during each of the conditions described above. Cardiac output was measured by thermodilution in patients without an intracardiac shunt. In those with shunts, O_2 consumption was measured (Waters Inc., model MM20, Rochester, Minnesota), and systemic and pulmonary blood flows were calculated using the Fick equation with inclusion of dissolved O_2. Errors related to sampling site variances were minimized by ensuring that, for each patient, venous samples were collected at the same site during each of the study conditions.

Delivery and monitoring of NO. Detailed descriptions of the technical aspects of our delivery of NO in both ventilated and spontaneously breathing patients have been published previously (11,12). We used NO gas (Scott Specialty Gases, Plumsteadville, Pennsylvania or BOC Gases, Murray Hill, New Jersey) of medical grade quality, which

Table 1. Diagnoses of Patients in Group 1 (n = 46)

Unrepaired Heart Disease (n = 26)	n	Repaired Heart Disease (n = 14)	n	Lung Pathology (n = 6)	n
VSD	5(1)	Complex single ventricle postpalliation	4(1)	Pulmonary emboli	3(2)
CAVC	5	TGA post Senning	3(1)	Restrictive lung disease (lupus)	1
Shone's syndrome	5	TGA/VSD post PAB	2	Primary pulmonary hypertension	1
PDA	2	TGA post Mustard	1	Cystic fibrosis	1
Cardiomyopathy	2	TGA post ASO	1(1)		
VSD with PDA	1	CAVC repair	1		
Truncus arteriosus	1	TOF/PA full repair	1		
ASD primum	1	ASD secundum	1		
ASD secundum with PDA	1				
Supracardiac TAPVC	1				
ASD secundum	1				
TGA/VSD	1				

In parentheses is the number of patients who did not respond to either oxygen or nitric oxide.
ASD = atrial septal defect; ASO = arterial switch operation; CAVC = complete atrioventricular canal; PAB = pulmonary artery band; PDA = patent ductus arteriosus; Shone's syndrome = multiple left-sided obstructive lesions; TAPVC = total anomalous pulmonary venous connection; TGA = transposition of the great arteries; TOF/PA = tetralogy of Fallot with pulmonary atresia; VSD = ventricular septal defect.

Table 2. Diagnoses of Patients in Group 2 (n = 25)

Unrepaired Heart Disease (n = 19)	n	Repaired Heart Disease (n = 3)	n	Lung Pathology (n = 3)	n
VSD	5	PDA	1	COPD	1(1)
CAVC	1	TAPVC with PV stenosis	1(1)	Primary pulmonary hypertension	1
Shone's syndrome	3	TOF/PA	1	Pulmonary emboli	1
PDA	1				
ASD secundum	4(1)				
VSD with mitral stenosis	2				
VSD with coarctation	1				
ASD primum	1				
Cardiomyopathy	1				

In parentheses is the number of patients who did not respond to either oxygen or nitric oxide in oxygen.
COPD = chronic obstructive pulmonary disease; PV = pulmonary vein; other abbreviations as in Table 1.

conformed to Food and Drug Administration standards. In the spontaneously breathing individuals NO was delivered using the titration technique from source tanks with an 800-ppm concentration. Flow rates greater than the patients' minute volumes were delivered through a one-way inspiratory valve to a face mask. The expired gases were scavenged using a reservoir bag and regulated wall suction. In the seven patients who were mechanically ventilated, ventilator settings were kept constant throughout the study. Nitric oxide, nitrogen dioxide (NO_2) and FiO_2 were continuously monitored from a sampling port at the airway (Thermoenvironmental Instruments Chemiluminescence model 42H, Franklin, Massachusetts or NOxBOX Electrochemical Inhaled NO Therapy Monitor, Bedfont Scientific USA, Medford, New Jersey). Peak measured NO_2 concentrations were recorded in all patients during delivery of the drug. Because there were no reports of methemoglobinemia during 15-min diagnostic trials of NO at 80 ppm (11), we eventually ceased to routinely measure methemoglobin levels during brief inhalations. Therefore, methemoglobin levels were obtained by cooximetry (CIBA-Corning model 2500, Medfield, Massachusetts) after 15 min in the first 22 of 46 patients in group 1 and not thereafter. Written informed consent was obtained from the patients or their parents under a protocol approved by the Clinical Investigation Committee of Children's Hospital and submitted to the Food and Drug Administration.

Statistical analysis and calculations. Results are presented as mean values ± SEM. Vascular resistances were calculated using standard equations and were expressed in Wood units corrected for body surface area ($U \cdot m^2$). Groups 1 and 2 were analyzed separately with patients in each group acting as their own controls. Repeated measures analysis of variance was used to look for differences in the measurements over the four study conditions in group 1 and the three conditions in group 2. If differences were found, then the Bonferroni multiple comparisons procedure was used to determine where differences existed. A p value <0.05 was considered significant.

RESULTS

Group 1: comparison of RA, O_2, RA and NO+RA. Pulmonary vascular resistance differed across the four conditions, ($p < 0.0001$) (Table 3). Oxygen decreased PVR from 17.2 ± 2.1 $U \cdot m^2$ to 11.1 ± 1.5 $U \cdot m^2$ ($p < 0.05$). Administration of inhaled NO at 80 ppm in RA caused a comparable decrease from 17.8 ± 2.2 $U \cdot m^2$ to 11.7 ± 1.7 $U \cdot m^2$ ($p < 0.05$) (Fig. 1). Comparison of the mean percentage decreases from RA to O_2 (36.9 ± 3.3%) and RA to NO+RA (35.1 ± 3.5%) revealed no difference by paired *t* test. Changes in pulmonary artery pressures may not reflect pulmonary vasodilation, because there were patients with intracardiac shunts. Nevertheless, the mean pulmonary artery pressure was significantly lower in both O_2 and NO+RA compared with RA despite increases in pulmonary blood flow in 21 of 23 patients with intracardiac shunts during treatment.

Mean systemic arterial pressure, systemic vascular resistance, right atrial pressure, left atrial pressure, heart rate, pH and P_{CO_2} did not change with administration of O_2 or NO. Arterial P_{CO_2} (Pa_{O_2}) increased from 66 ± 3 mm Hg in RA to 278 ± 23 mm Hg with 100% O_2; however, there was no significant difference in Pa_{O_2} between RA and NO+RA (68 ± 4 vs. 73 ± 4 mm Hg).

Using a reduction in PVR of 20% or more as a marker for responsiveness, we compared individual patient results to O_2 and NO+RA (Fig. 2). Oxygen caused a positive response in 36/46 patients. Of the 10 nonresponders, four responded with a 20% or more decrease to NO. Nitric oxide in RA caused a positive response in 32/46. Of the 14 nonresponders to NO+RA, eight responded to O_2. Six patients did not respond to either vasodilator (Table 1).

The peak NO_2 level was recorded in all 46 patients and was 1.3 ± 0.2 ppm. Methemoglobin measured at the conclusion of the 15-min period of NO inhalation in 22/46 patients was 0.8 ± 0.1%.

Group 2: comparison of RA, O_2 and NO+O_2. Pulmonary vascular resistance differed across the three conditions ($p < 0.0001$) (Table 4). Pulmonary vascular resistance

Table 3. Hemodynamic Data for Group 1

Variable (mean ± SEM)	A: RA	B: Oxygen	C: RA	D: NO+RA	ANOVA p Value
PVR (U·m^2)	17.2 ± 2.1	11.1 ± 1.5	17.8 ± 2.2	11.7 ± 1.7	< 0.0001*†
mPAp (mm Hg)	62.7 ± 3.3	54.9 ± 3.1	60.9 ± 3.4	51.2 ± 3.0	< 0.0001*†
LAp (mm Hg)	13.7 ± 0.8	14.6 ± 1.0	14.0 ± 0.9	14.9 ± 1.1	0.05
CI (liters/min/m^2)	3.6 ± 0.3	3.2 ± 0.2	3.5 ± 0.2	3.3 ± 0.2	0.19
RAp (mm Hg)	9.0 ± 0.5	9.1 ± 0.5	8.8 ± 0.5	8.4 ± 0.5	0.08
MAP (mm Hg)	79.2 ± 2.3	81.0 ± 2.3	79.5 ± 2.6	79.4 ± 2.6	0.55
SVR (U·m^2)	24.2 ± 1.8	25.7 ± 1.6	24.2 ± 1.8	24.8 ± 1.7	0.33
pH	7.36 ± 0.01	7.36 ± 0.01	7.35 ± 0.01	7.35 ± 0.01	0.43
P_{CO_2}	41.6 ± 1.1	41.2 ± 1.0	41.8 ± 1.1	43.0 ± 1.2	0.07
P_{O_2}	65.6 ± 2.7	277.6 ± 23.2	68.1 ± 3.6	73.5 ± 3.5	< 0.0001*
Heart rate	108 ± 4	107 ± 4	104 ± 5	105 ± 5	0.24

*Variable in oxygen (B) is different than in room air (A) ($p < 0.05$). †Variable in nitric oxide (D) is different than in room air (C) ($p < 0.05$).

ANOVA = analysis of variance; CI = cardiac index; LAp = left atrial pressure; MAP = mean arterial blood pressure; mPAp = mean pulmonary artery pressure; P_{CO_2} = partial pressure of carbon dioxide; P_{O_2} = partial pressure of oxygen; PVR = pulmonary vascular resistance; RA = room air; RAp = right atrial pressure; SVR = systemic vascular resistance.

decreased from 20.1 ± 2.6 U·m^2 in RA to 14.3 ± 1.9 U·m^2 in O_2 and further to 10.5 ± 1.7 U·m^2 in NO+O_2 (Fig. 3). Pulmonary vascular resistance was significantly lower in O_2 compared to RA ($p < 0.05$). The PVR with combination therapy was statistically lower than that measured in air or in O_2 ($p < 0.05$ for both). Oxygen caused a reduction in PVR from baseline of 20% or more in 16 of 25 patients. Of the remaining nine patients, six responded with a 20% or more decrease when inhaling NO+O_2. Three patients did not have a positive response to either O_2 or the combination of O_2 and NO (see Table 2). Using the McNemar's test, if responsiveness differed between the two treatments, patients were more likely to respond to NO+O_2 than to O_2 alone ($p = 0.01$). Ten of the 25 patients underwent complete surgical repair of their cardiac defects within 1 month of their catheterization. Those 10 patients had a baseline PVR in RA of 12.9 ± 1.9 U·m^2 that decreased to 7.1 ± 1.9 U·m^2 in O_2 and to 4.1 ± 1.9 U·m^2 in NO+O_2. Each patient undergoing surgical repair had a baseline PVR in RA >6 U·m^2. Five of 10 had PVR >6 U·m^2 in O_2, but only one had PVR >6 U·m^2 in NO+O_2. All 10 patients survived and were discharged home on median postoperative day 5.5, range 4 to 29.

Mean pulmonary artery pressure decreased from 63.4 ± 3.7 mm Hg in RA to 57.7 ± 3.5 mm Hg in O_2 to 50.6 ± 3.5 mm Hg in NO+O_2. This occurred despite an increase in pulmonary blood flow in 13 of 15 patients with shunts. The pulmonary artery pressure with NO+O_2 was significantly lower than that measured in air or in O_2 ($p < 0.05$ for both). There was no difference between left atrial pressure in RA and in O_2. Left atrial pressure was significantly higher in NO+O_2 (15.5 ± 1.3 mm Hg) than in RA (13.1 ± 1.1 mm Hg) or O_2 (12.7 ± 1.0 mm Hg).

Mean systemic blood pressure increased over the three study conditions, from 76.8 ± 2.9 mm Hg in RA to 80.6 ± 2.5 mm Hg in O_2 to 83.4 ± 2.6 mm Hg in NO+O_2. Blood pressure was significantly higher in NO+O_2 than in RA, but not statistically different from blood pressure in O_2. Cardiac index, systemic vascular resistance, right atrial pressure, heart rate, pH and P_{CO_2} did not change. Arterial

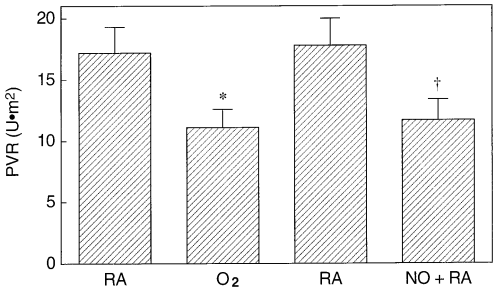

Figure 1. Pulmonary vascular resistance (PVR) (mean ± SE) differed across the four study conditions in group 1 ($p < 0.0001$); PVR was lower in oxygen (O_2) compared with room air (RA) (*) and was lower in nitric oxide in RA (NO+RA) compared with RA (†) ($p < 0.05$ for both).

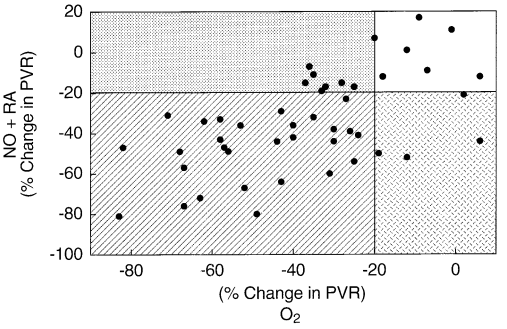

Figure 2. Individual patients' percentage change in PVR with O_2 is plotted against percentage change in PVR with NO+RA. Using a 20% decrease in PVR as a marker for responsiveness, some patients responded to one drug only. Neither O_2 nor NO+RA identified all patients with pulmonary vasoreactivity. Abbreviations as in Figure 1.

Table 4. Hemodynamic Data for Group 2

Variable (mean ± SEM)	A: RA	B: Oxygen	C: NO+O_2	ANOVA p Value
PVR (U·m^2)	20.1 ± 2.6	14.3 ± 1.9	10.5 ± 1.7	< 0.0001*†‡
mPAp (mm Hg)	63.4 ± 3.7	57.7 ± 3.5	50.6 ± 3.5	0.0002†‡
LAp (mm Hg)	13.1 ± 1.1	12.7 ± 1.0	15.5 ± 1.3	0.002†‡
CI (liter/min/m^2)	3.1 ± 0.3	3.2 ± 0.3	3.2 ± 0.3	0.93
RAp (mm Hg)	8.0 ± 0.7	8.3 ± 0.8	8.4 ± 0.7	0.78
MAP (mm Hg)	76.8 ± 2.9	80.6 ± 2.5	83.4 ± 2.6	0.004‡
SVR (U·m^2)	26.8 ± 2.7	28.1 ± 2.6	29.8 ± 3.0	0.34
pH	7.38 ± 0.01	7.36 ± 0.01	7.36 ± 0.01	0.08
P_{CO_2}	38.8 ± 1.2	39.7 ± 1.5	40.5 ± 1.7	0.27
P_{O_2}	67.3 ± 3.9	277.6 ± 30.4	302.8 ± 27.9	< 0.0001*‡
Heart rate	108 ± 4	107 ± 4	105 ± 5	0.58

*Variable in oxygen (B) is different than in room air (A) ($p < 0.05$). †Variable in NO+O_2 (C) is different than in oxygen (B) ($p < 0.05$). ‡Variable in NO+O_2 (C) is different than in room air (A) ($p < 0.05$). Abbreviations as in Table 3.

partial pressure of O_2 was significantly higher both in O_2 and in NO+O_2 as compared with RA. Arterial partial pressure of O_2 was not different in NO+O_2 compared with O_2 (302.8 ± 27.9 vs. 277.6 ± 30.4 mm Hg). The peak NO_2 level during NO delivery was 2.3 ± 0.3 ppm.

DISCUSSION

We compared the inhaled vasodilators O_2 and NO in 71 patients during acute vasodilator testing at cardiac catheterization. In 46 patients, 100% O_2 and inhaled NO at 80 ppm in air produced comparable and selective decreases in mean pulmonary artery pressure and PVR. However, O_2 or NO used separately failed to identify all patients with a significant capacity for pulmonary vasodilation. The combination of NO (80 ppm) with 91% O_2 in an additional group of 25 patients produced significantly more pulmonary vasorelaxation compared with O_2 used alone. In 22/25 patients there was a positive pulmonary vasodilator response during combination therapy compared to only 16/25 when breathing O_2 alone. None of the 71 patients studied showed any evidence of toxicity from either drug during the brief period of this diagnostic trial. Our data suggest that combination testing with NO in O_2 provides additional pulmonary vasodilation, can be safely and accurately delivered to patients during diagnostic cardiac catheterization and can rapidly identify patients with pulmonary vasoreactivity. The combination of agents appears to identify patients with significant pulmonary vasoreactivity who might not be recognized if O_2 or NO were used separately.

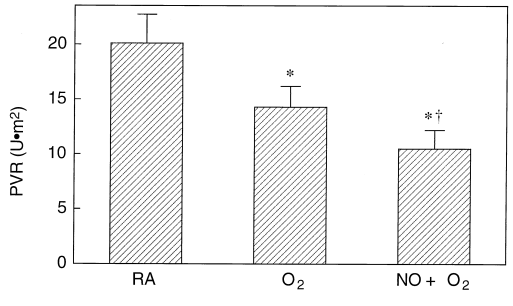

Figure 3. Pulmonary vascular resistance (mean ± SE) differed across the three study conditions in group 2 ($p < 0.0001$); PVR was lower in O_2 compared with RA (*) and was lower in NO+O_2 compared with RA (*) and O_2 (†) ($p < 0.05$ for all comparisons). Abbreviations as in Figure 1.

Importance of vasodilator testing. The precise stage when pulmonary vascular disease has progressed to a point where surgical repair of congenital heart lesions cannot be safely performed is unknown. Morphologic criteria (2) and pulmonary hemodynamics (13) are useful, but imprecise. Pulmonary vascular resistance calculated to be more than 6 to 8 U·m^2 has been shown to be associated with poor operative outcome regardless of lung histology (1,4,14). In contrast, patients who respond to vasodilators with a PVR less than 6 to 8 U·m^2 do well postoperatively (13). Demonstration of a reactive pulmonary bed in patients being evaluated for transplantation has enabled patients to be offered a single organ heart instead of heart–lung block with successful results (15). Patients with elevated resistance but reactive pulmonary vasculature may need more intensive postoperative care and presumably would be excellent candidates for NO therapy in the postoperative period should pulmonary hypertension emerge. Response to acute vasodilator testing in patients with primary pulmonary hypertension is an important marker for survival (3) and may identify patients who would benefit from chronic medical therapy (5,6).

Comparison with other studies. Prior research in children with pulmonary hypertension has shown that O_2 failed to unmask all reversible pulmonary vasoconstriction (3,10). Prostacyclin administration in patients with pulmonary hypertension breathing O_2 caused further pulmonary vasodilation. However, prostacyclin can cause systemic side effects including tachycardia and hypotension (16). Previous studies of vasoreactivity in children during cardiac catheterization found variable responsiveness to NO that seemed to

parallel the progression of established vascular disease (17). Studies examining the efficacy of NO in O_2, including recent work by Allman and colleagues, have suggested differences between the responses to NO, O_2 and/or the combination of agents (18–20). Each prior study, however, has had insufficient power to establish a significant difference in PVR.

Nitric oxide causes vasorelaxation through a cyclic guanosine monophosphate–mediated pathway. The mechanism of vasorelaxation caused by O_2 is not clearly known (21). The fact that some patients responded to one agent with significant vasodilation but not the other, and that the majority of patients experienced increased vasodilation with combination therapy compared with O_2 alone, suggests that the mechanisms may not be identical.

Potential toxicities. The major recognized toxicities associated with inhaling NO are cytotoxic effects in the lung due to exposure to excess NO_2 and methemoglobinemia due to the intravascular binding to hemoglobin. Nitrogen dioxide will develop in delivery systems at a rate that is proportional to NO and O_2 concentrations and contact times between the two gases. When NO was delivered with maximal amounts of O_2 in this study, NO_2 levels averaged 2.3 ± 0.3 ppm, below the accepted environmental exposure level of 5 ppm (22). Nitrogen dioxide should be continuously monitored, especially in patients mechanically ventilated with circuits that do not use continuous gas flows. If patients receive prolonged treatment with NO in high concentrations of O_2, we recommend reduction in the NO dose to diminish potential dose-related toxicity. There have been no reports of clinically significant methemoglobinemia during brief exposure to NO at doses as high as 80 ppm. Methemoglobin measured at the conclusion of the 15-min period of NO inhalation in 22/46 patients was 0.8 ± 0.1%. This along with previously published results (11) supports the contention that routine measurement of methemoglobin may be unnecessary during brief diagnostic trials of NO.

It is notable that the combination of NO in O_2 resulted in an increase in left atrial pressure compared with RA or O_2 alone. Reports have suggested that O_2 (23) or NO (24) may have deleterious effects to patients with heart failure. In this study no patient demonstrated clinically important pulmonary edema, hemodynamically significant systemic vasoconstriction or decreased cardiac index during the brief administration of O_2 or NO in O_2. Nevertheless, we believe that NO, especially when used with O_2, should be carefully monitored in patients with elevated left atrial pressures due to the potential induction of pulmonary edema.

Study limitations. The patient population studied was quite heterogeneous. However, this accurately reflects the typical spectrum of patients presenting for vasodilator testing during cardiac catheterization. Subgroup analysis of patients with congenital heart disease showed no differences in response compared to the group as a whole. Patients with lung pathology analyzed separately showed similar results, but numbers were too small to form conclusions. Subgroup analysis of patients with left to right shunts did not reveal any difference in response compared to those without shunts. The definition of responder and nonresponder is arbitrary, but a 20% change is often used in drug testing as a marker of responsiveness. There was no apparent predictive marker in patients who responded to one agent but not the other. It may be that repeated exposure to O_2 or NO would minimize differences between responders and nonresponders. Nonetheless, a single exposure to a drug is the common catheterization protocol. Limited information exists concerning optimal dosing of NO, with some investigators showing maximal vasodilation at doses as low as 2 ppm (19), and others demonstrating a dose–response relationship up to 80 ppm in a similar population (18). This study was designed as a brief diagnostic trial in a catheterization laboratory to determine the most effective and inclusive method of identifying patients with pulmonary vasoreactivity. Accordingly, 80 ppm was used during this brief testing with the appreciation that, if delivered for prolonged periods, it may be associated with dose-related increased toxicity. This study was not designed to demonstrate differences in long-term patient outcomes or clinical value of vasodilator testing. Maximal vasodilatory capacity may be of limited clinical value in some patients. Nevertheless, as a result of information acquired during combination therapy, some patients were offered surgery who did not respond to NO or O_2 alone; all patients survived.

Summary. Individually, NO and O_2 produced significant and comparable selective pulmonary vasodilation in a heterogeneous group of patients presenting to cardiac catheterization for pulmonary vasodilator testing. However, neither agent used separately identified all patients with the capacity to relax their pulmonary vascular bed. The combination of NO+O_2 caused significantly greater pulmonary vasodilation compared to O_2 and identified patients who had pulmonary vasoreactivity that was not appreciated during O_2 breathing alone. This study suggests that combination testing with NO+O_2 provides additional pulmonary vasodilation in patients with a reactive pulmonary vascular bed in a specific, safe and expeditious fashion during cardiac catheterization. Nitric oxide in O_2 distinguishes patients with significant pulmonary vasoreactivity who might not be identified using either agent separately.

Acknowledgments

We are grateful to John F. Keane, MD for his critical review of the manuscript and to Kimberlee Gauvreau, ScD for her expert assistance with statistical analysis.

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