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Inhaled Nitric Oxide Selectively Dilates Pulmonary Vasculature in Adult Patients With Pulmonary Hypertension, Irrespective of Etiology

Richard A. Krasuski, MD,* John J. Warner, MD,* Andrew Wang, MD,* J. Kevin Harrison, MD,* Victor F. Tapson, MD,† Thomas M. Bashore, MD*

Durham, North Carolina

OBJECTIVES We sought to compare the responses of patients with pulmonary hypertension from primary and secondary causes (PPH and SPH, respectively) to inhaled nitric oxide (iNO) in the cardiac catheterization laboratory.

BACKGROUND Pulmonary hypertension can lead to right ventricular pressure overload and failure. Although vasodilators are effective as therapy in patients with PPH, less is known about their role in adults with SPH. Inhaled nitric oxide can accurately predict the response to other vasodilators in PPH and could be similarly utilized in SPH.

METHODS Forty-two patients (26 to 77 years old) with pulmonary hypertension during cardiac catheterization received iNO. Demographic and hemodynamic data were collected. Their response to iNO was defined by a decrease of ≥20% in mean pulmonary artery (PA) pressure or pulmonary vascular resistance (PVR).

RESULTS Mean PA pressures and PVR were lower during nitric oxide (NO) inhalation in all patients with pulmonary hypertension. Seventy-eight percent of patients with PPH and 83% of patients with SPH were responders to iNO. A trend was seen toward a greater response with larger doses of NO in patients with SPH. Nitric oxide was a more sensitive predictor of response (79%), compared with inhaled oxygen (64%), and was well tolerated, with no evidence of systemic effects. Elevation in right ventricular end-diastolic pressure appeared to predict poor vasodilatory response to iNO.

CONCLUSIONS Nitric oxide is a safe and effective screening agent for pulmonary vasoreactivity. Regardless of etiology of pulmonary hypertension, pulmonary vasoreactivity is frequently demonstrated with the use of NO. Right ventricular diastolic dysfunction may predict a poor vasodilator response. (J Am Coll Cardiol 2000;36:2204–11) © 2000 by the American College of Cardiology

Primary pulmonary hypertension (PPH) is a devastating disease affecting a young, predominantly female population in the prime of their lives. Progressive dyspnea, hypoxemia and chest pain eventually give way to ascites, peripheral edema and generalized anasarca (massive edema). The development and demonstrated efficacy of pulmonary vasodilating agents, including calcium channel blockers and, more recently, continuous intravenous prostacyclin has given hope to these unfortunate patients (1–3).

Demonstration of a positive response to vasodilating agents in PPH has been shown to correlate with an improved long-term clinical outcome (4). A number of vasodilating agents have been used in the cardiac catheterization laboratory, including adenosine, atrial natriuretic peptide, amrinone, isoproterenol, tolazoline, nitroprusside, nitroglycerin, hydralazine, prostacyclin and calcium channel antagonists, in an attempt to assess these patients and decide on long-term therapy.

From the *Division of Cardiology and †Division of Pulmonary and Critical Care, Department of Medicine, Duke University Medical Center, Durham, North Carolina.

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Inhaled nitric oxide (iNO) has many characteristics that render it an excellent vasodilator for the pulmonary vascular bed. Because it is delivered as a gas and is rapidly inactivated when bound to hemoglobin, the effects remain local, and hypotension is exceedingly rare. Its short half-life also permits rapid discontinuation, if necessary.

Nitric oxide (NO) is critical in the regulation of intrinsic pulmonary vascular tone (5), and pulmonary hypertension, at least in part, results from a derangement in the regulation of NO. Most of the published data on the use of iNO in the catheterization laboratory relates to patients with PPH or to children with congenital heart defects that result in increased pulmonary vascular blood flow and resistance. However, most patients with pulmonary hypertension in the U.S. are a heterogeneous group of adults with progressive pulmonary and cardiac disease (secondary pulmonary hypertension [SPH]) (6). These patients are also at risk for progressive right ventricular pressure overload and eventually cor pulmonale. As in the PPH population, this complication can significantly affect quality of life and hasten mortality. Unfortunately, the only therapy demonstrated to prolong survival in patients with end-stage lung disease is inhaled oxygen (7,8).

Abbreviations and Acronyms

iNO	= inhaled nitric oxide
NO	= nitric oxide
NO_2	= nitric dioxide
NYHA	= New York Heart Association
PA	= pulmonary artery
PPH	= primary pulmonary hypertension
PVR	= pulmonary vascular resistance
RVEDP	= right ventricular end-diastolic pressure
SPH	= secondary pulmonary hypertension
SVR	= systemic vascular resistance

The efficacy and safety of iNO in adults with SPH has not yet been fully clarified. The objective of this study was to compare the responses of patients with PPH and SPH to iNO. Previous studies have been divided concerning the ideal dose of NO and the absence or presence of a dose response; we sought to determine if a dose response existed (9–13).

METHODS

Study group. Patients with pulmonary hypertension (defined by a mean pulmonary artery [PA] pressure ≥25 mm Hg at the time of cardiac catheterization) were enrolled between November 1998 and November 1999. Written, informed consent was obtained by using a protocol approved by Duke University Medical Center's Investigations Review Board. Patients with PPH, as defined by the National Institutes of Health (NIH, Bethesda, Maryland) criteria (14), had previously undergone extensive evaluation to exclude any secondary causes of their pulmonary hypertension before cardiac catheterization. Patients underwent cardiac catheterization expressly for vasodilator testing or as part of their diagnostic work-up before a further intervention (i.e., lung transplantation evaluation or before congenital defect repair). Forty-two patients had complete hemodynamic assessment and vasodilator testing with NO.

Hemodynamic assessment. All studies were conducted in the fasting state with minimal sedation. If the patient was taking oral vasodilating drugs, this was noted, but doses were not withheld. If left heart catheterization was performed, all contrast injections were performed before baseline hemodynamic assessment. Right heart catheterization was performed using a single end-hole, balloon flotation catheter (Bard Pulmonary Wedge Catheter, Medtronic, Minneapolis, Minnesota). Baseline hemodynamic measurements included mean right atrial pressure, right ventricular systolic and diastolic pressures, PA systolic, diastolic and mean pressures, mean pulmonary capillary wedge pressure and femoral artery systolic, diastolic and mean pressures. Repeat measurements during drug delivery included PA systolic, diastolic and mean pressures, mean pulmonary capillary wedge pressure and femoral artery systolic, diastolic and mean pressures.

Blood samples were obtained from the main PA and femoral artery for calculation of the cardiac output, using an assumed Fick method. In patients with an intracardiac shunt, two right heart catheters were placed, and a blood sample of the superior vena cava was obtained to estimate the mixed venous oxygen saturation. Systemic and pulmonary vascular resistances (SVR and PVR) were calculated using standard hemodynamic equations and are presented in absolute (Wood) units.

NO delivery protocol and vasodilator response. The techniques for delivery of NO have been well described previously (15). Nitric oxide gas (INO Therapeutics, Madison, Wisconsin) of medical-grade quality and conforming to Food and Drug Administration standards was used. A specialized delivery device (INOvent Delivery System, Ohmeda Inc., Madison, Wisconsin) delivered NO from source tanks to achieve proper dosing. Flow rates were maintained at a rate greater than the patients' minute ventilation through a one-way valve into a specially designed face mask. Levels of NO, oxygen and nitrogen dioxide (NO_2) were continuously monitored throughout the procedure from a sampling port just proximal to the airway. Because of previous studies demonstrating a negligible amount of methemoglobinemia with short-term inhalation of larger doses of NO (16), methemoglobin levels were not routinely measured.

All patients received iNO at doses of 10, 20 and 40 parts per million (ppm). Five minutes was allowed at each iNO dose before hemodynamic assessment was undertaken, and PA and femoral artery blood samples were drawn for Fick cardiac output determination. Repeated measurements showed a maximal response within this period, with very little variability between measures. Patients could subsequently receive 100% oxygen by a non-rebreather face mask at the discretion of the performing physician.

A significant response to vasodilator testing was defined as a drop in the mean PA pressure of ≥20% or a decrease of ≥20% in PVR.

Statistical analysis. Data are presented as the mean value ± SD for continuous variables, and as the number (percentage) for discrete variables. Comparison of dichotomous variables was performed using the chi-square test or the Fisher exact test, as appropriate. Comparisons of the change from baseline in individual measures were made using the paired *t* tests. The dose–response curves for PVR and mean PA pressures were evaluated by comparing measures at baseline, 10 ppm, 20 ppm and 40 ppm for PPH and SPH, using univariate repeated measures techniques. For each outcome, a model was developed that included as covariates the pulmonary hypertension type (primary vs. secondary), the intrasubject effect of PPH versus SPH, the dose and the interaction between pulmonary hypertension type and dose. Contrast tests were used to examine the change in outcome with increments in dose. Changes from baseline to 10 ppm, from 10 to 20 ppm and from 20 to 40 ppm were tested for patients with PPH and SPH separately. To correct for multiple comparisons, a Bonferroni correc-

Table 1. Baseline Clinical and Hemodynamic Data of Patients Receiving NO

	PPH (n = 18)	SPH (n = 24)	p Value
Demographic data			
Age (yrs)	55 ± 14	55 ± 11	0.919
Female (%)	78%	67%	0.506
Pulmonary vasodilator therapy (%)	33%	54%	0.179
NYHA functional class	2.94 ± 0.64	2.55 ± 0.67	0.064
Hemodynamic data			
Mean RAP (mm Hg)	10.4 ± 6.3	12.1 ± 4.6	0.306
Systolic RVP (mm Hg)	78.3 ± 30.7	66.4 ± 20.5	0.141
Diastolic RVP (mm Hg)	13.6 ± 7.0	15.3 ± 6.8	0.438
Mean PAP (mm Hg)	51.5 ± 19.8	42.8 ± 11.5	0.106
Mean PCWP (mm Hg)	10.5 ± 3.4	13.8 ± 6.1	0.032
Mean AoP (mm Hg)	105.2 ± 15.8	103.2 ± 14.2	0.676
Cardiac output (liters/min)	4.1 ± 1.1	5.2 ± 1.8	0.025
PVR (Wood U)	11.3 ± 8.2	6.2 ± 3.8	0.022
SVR (Wood U)	24.0 ± 5.7	20.8 ± 6.8	0.108
Oxygen saturation (%)			
PA	60.3 ± 10.4	66.2 ± 10.6	0.078
Aortic	91.2 ± 4.8	92.4 ± 6.2	0.050

Data are presented as the mean value ± SD or percentage of patients.
AoP = aortic pressure; NYHA = New York Heart Association; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PPH = primary pulmonary hypertension; PVR = pulmonary vascular resistance; RAP = right atrial pressure; RVP = right ventricular pressure; SPH = secondary pulmonary hypertension; SVR = systemic vascular resistance.

tion was applied, and significance was declared at $p < 0.008$ (0.05/6) for each outcome. For all other individual comparisons, statistical significance was assumed at $p < 0.05$. All analyses were performed using SAS (SAS Institute, Cary, North Carolina).

RESULTS

Patient group. Forty-three patients were enrolled in the protocol between November 1998 and November 1999. One patient was unable to tolerate the face mask because of anxiety and withdrew from the study. Of the remaining 42 patients, 18 had PPH (43%) and 24 had SPH (57%). The patients' ages ranged from 26 to 77 years.

The etiologies of pulmonary hypertension in the SPH group are listed in Table 1. Intrinsic pulmonary disease was the cause in 17 patients (71%), and chronic obstructive disease was the cause in 8 (33%) of 24 patients. Five patients (21%) with atrial septal defects (four with secundum atrial septal defect and one with sinus venosus atrial septal defect with an anomalous pulmonary vein) underwent vasodilator testing to evaluate their potential for vasoreactivity.

Demographic data and baseline hemodynamic variables. Baseline demographic data (Table 1) did not differ significantly between the two groups. A trend was seen toward poorer functional class in the PPH group compared with the SPH group (mean New York Heart Association [NYHA] congestive heart failure class 2.94 vs. 2.55, respectively; $p = 0.06$). More patients with SPH were taking agents with potential pulmonary vasodilating effects (nifedipine, amlodipine, diltiazem, verapamil and isosorbide dinitrate), with the primary indication of systemic hypertension. The mean PA and aortic pressures did not differ between patients taking vasodilators and those not taking vasodilators. Right heart pressures tended to be slightly higher in patients with PPH (Table 1), but did not reach statistical significance. Patients with SPH had significantly higher pulmonary capillary wedge pressures (13.8 vs. 10.5 mm Hg, $p = 0.03$) and greater cardiac output (5.15 vs. 4.12 liters/min, $p = 0.03$). The PVR was higher in the PPH group (11.3 vs. 6.2 Wood units, $p = 0.02$).

Response to NO inhalation. Fourteen (78%) of 18 patients with PPH were responders and 20 (83%) of 24 patients with SPH were responders to iNO (Table 2) ($p = 0.706$ for comparison between the groups). All doses of NO (10, 20 and 40 ppm) significantly lowered mean PA pressures in both groups (Table 3). The greatest decrement in PA pressure occurred with the lowest dose of drug. Patients with PPH had the majority of their vasoreactive response at 10 ppm of NO, with little additional vasodilation apparent at the higher doses. Of interest, patients with SPH had an additional vasodilatory response at each higher incremental dose (Fig. 1). At 10 ppm of NO, 13 (54%) of 24 patients with SPH were identified as responders. This increased to 15 (63%) of 24 patients with 20 ppm of NO and 20 (83%) of 24 patients with 40 ppm of NO. In contrast, 12 (67%) of 18 patients with PPH were responders at 10 ppm; and 20 and 40 ppm only increased the number of responders to 14 (78%) of 18 patients.

Because more patients in the SPH group were taking vasodilators, the response to NO was compared between patients taking vasodilators at baseline (diltiazem, verapamil, amlodipine, nifedipine and isosorbide dinitrate) and patients not taking vasodilators. No discernable difference in vasodilator response was seen.

Because right ventricular dysfunction may provide a surrogate for chronicity or severity of disease, right ventricular end-diastolic pressure (RVEDP) was compared with the extent of mean PA pressure improvement during inhalation of 40 ppm of NO. No patient experienced a significant (≥20%) decrease in PA pressure if their RVEDP exceeded 20 mm Hg. With RVEDP ≤10, 9 (82%) of 11 patients experienced a significant decrease in PA pressure. Of the patients with intermediate RVEDP (12 to 20 mm Hg), 68% experienced a response.

When hemodynamic variables at 40 ppm of iNO were compared with baseline values (Table 4), significant lowering of the mean PA pressure and PVR was noted in both groups. The aortic and PA saturations increased in both groups, as well. No effect on the systemic pressures or SVR was noted in either group. The cardiac output between baseline and peak iNO concentration also did not significantly change in either group.

Inhaled NO was well tolerated, and no complications (such as bradycardia, hypotension, chest pain or altered

Table 2. Vasodilator Response to Inhaled NO

Diagnosis	No. of Patients	PAP* Responders	PVR† Responders	PVR or PAP	PVR and PAP
PPH	18	12 (67%)	13 (72%)	14 (78%)	11 (61%)
SPH	24	15 (63%)	18 (75%)	20 (83%)	13 (54%)
Intrinsic pulmonary disease	17	10 (59%)	14 (78%)	15 (82%)	9 (53%)
COPD	8	4 (50%)	6 (75%)	7 (88%)	3 (38%)
Pulmonary fibrosis	3	2 (67%)	3 (100%)	3 (100%)	2 (67%)
Sarcoidosis	2	1 (50%)	2 (100%)	2 (100%)	1 (50%)
CREST syndrome	3	2 (67%)	2 (67%)	2 (67%)	2 (67%)
Methotrexate toxicity	1	1 (100%)	1 (100%)	1 (100%)	1 (100%)
Cardiac disease	7	5 (71%)	4 (57%)	5 (71%)	4 (57%)
Peripheral PA stenosis	1	1 (100%)	0 (0%)	1 (100%)	0 (0%)
Mitral regurgitation	1	1 (100%)	1 (100%)	1 (100%)	1 (100%)
Atrial septal defect	5	3 (60%)	3 (60%)	3 (60%)	3 (60%)

* Pulmonary artery pressure (PAP) response to inhaled nitric oxide is defined by a decrease in mean pulmonary artery pressure of ≥20%.

† Pulmonary vascular resistance (PVR) response is defined by a decrease in PVR of ≥20%. Because of controversy regarding the true definition of the response to a pulmonary vasodilator, data for the various reported definitions are listed. Data are presented as number (%) of patients.

COPD = chronic obstructive pulmonary disease; CREST = variant of scleroderma; PA = pulmonary artery; PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; PPH = primary pulmonary hypertension; SPH = secondary pulmonary hypertension.

mental state) were apparent in any patient receiving iNO. Inspired levels of NO_2 (a toxic metabolite of NO) were closely monitored during NO inhalation and did not exceed 1.0 ppm, well below reported toxic levels (17).

Response to 100% oxygen by face mask versus iNO. Fourteen patients (five with PPH and nine with SPH) also received a trial of 100% oxygen by a non-rebreather face mask. Comparable data for these patients with 40 ppm of iNO versus 100% oxygen are listed in Table 5.

Overall, 64% of patients were responders (≥20% decrease in mean PA pressure or ≥20% decrease in PVR) to 100% oxygen, and 79% were responders to iNO. Three of the patients who did not respond to oxygen responded to NO. One of the patients who did not respond to NO responded to oxygen.

DISCUSSION

In 1980, Furchgott and Zawadzki (18) first described the importance of an intact endothelium in relation to the regulation of vascular smooth muscle tone. The endothelium-derived relaxation factor involved in this regulation was identified as NO in 1987 (19). Since that time, an explosion in NO research has led to a clearer understanding of the importance of this molecule in normal and abnormal human physiology.

Nitric oxide has been demonstrated to be an important intercellular and intracellular messenger molecule in virtually every organ in the body (20). It regulates basal systemic and pulmonary artery tone in healthy humans (21–23), and experimental models of pulmonary hypertension can be

Table 3. Response of Patients to Each Administered Dose of Inhaled NO

	PPH Group	SPH Group	All Patients
Baseline			
Mean PAP (mm Hg)	51.5 ± 4.7	42.8 ± 2.4	46.5 ± 2.5
PVR (Wood U)	11.3 ± 1.9	6.2 ± 0.8	8.4 ± 1.0
100 ppm iNO			
Mean PAP (mm Hg)	42 ± 4.1	37.1 ± 2.5	39.3 ± 2.3
10 ppm iNO vs. baseline	<0.001	<0.001	<0.001
PVR (Wood U)	8.4 ± 1.6	5.0 ± 0.7	6.5 ± 0.8
10 ppm iNO vs. baseline	<0.001	<0.001	<0.001
20 ppm iNO			
Mean PAP (mm Hg)	40.8 ± 4.3	35.6 ± 2.4	37.9 ± 2.3
20 ppm iNO vs. 10 ppm iNO	0.223	0.156	0.065
PVR (Wood U)	8.1 ± 1.6	4.6 ± 0.6	6.2 ± 0.8
20 ppm iNO vs. 10 ppm iNO	0.536	0.275	0.236
40 ppm iNO			
Mean PAP (mm Hg)	40.1 ± 4.5	33.8 ± 2.3	36.5 ± 2.3
40 ppm iNO vs. 20 ppm iNO	0.542	0.082	0.110
PVR (Wood U)	8.1 ± 1.9	4.4 ± 0.6	6.0 ± 0.9
40 ppm iNO vs. 20 ppm iNO	0.990	0.467	0.623

Data are presented as the mean value ± SD, with p value below.

iNO = inhaled nitric oxide; ppm = parts per million; other abbreviations as in Table 1.

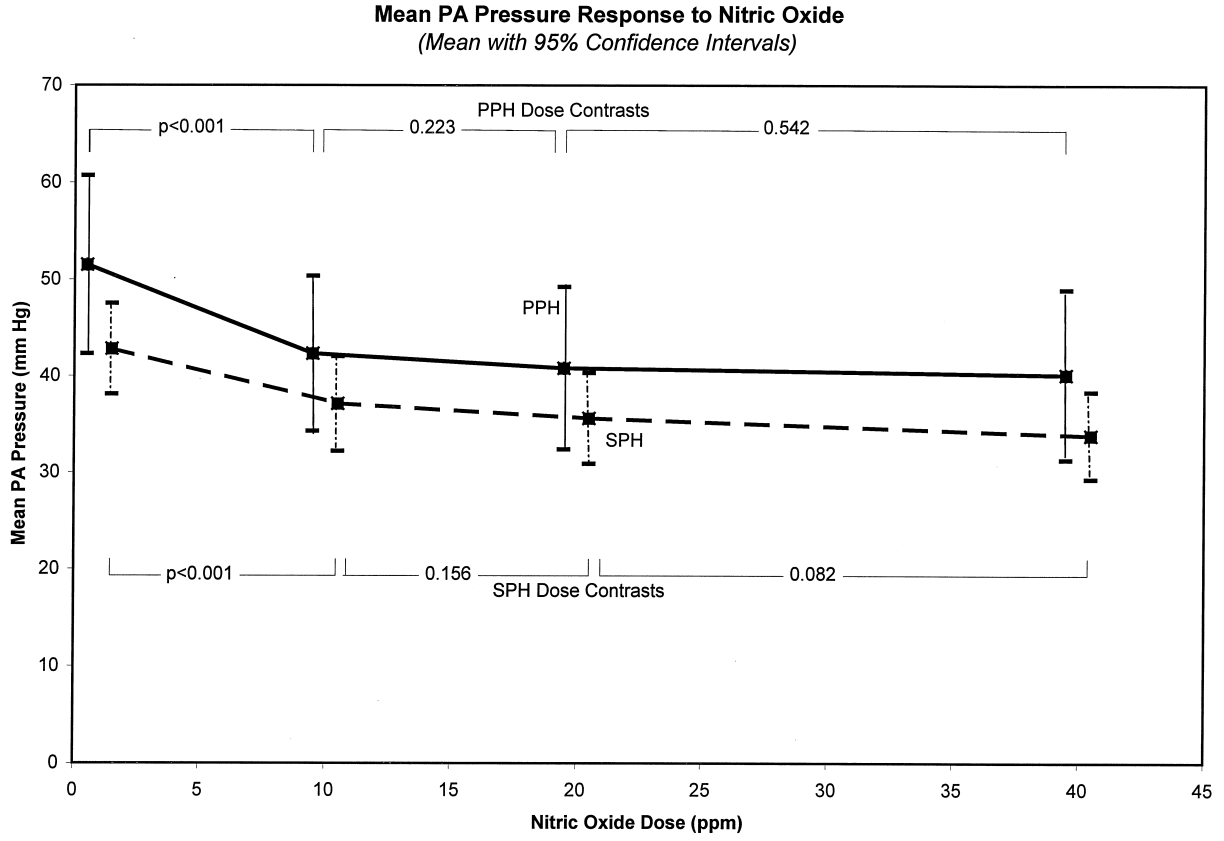

Figure 1. Response to iNO. The majority of the response is seen at 10 ppm of NO in both groups. However, patients with SPH show a trend toward a further pressure reduction with higher doses of iNO.

created through NO deprivation and inhibition (24,25). Nitric oxide was first administered to patients with pulmonary hypertension in 1991 (26). Since that time, it has been studied in a diagnostic or therapeutic role in a variety of disorders involving the pulmonary vasculature, including primary pulmonary hypertension (27,28); persistent pulmonary hypertension of the newborn (29,30); congestive heart failure (31,32); intrinsic pulmonary disease, including pulmonary fibrosis (33), scleroderma (34) and chronic obstructive pulmonary disease (35,36); acute respiratory distress syndrome (37,38); and a variety of corrected and uncorrected congenital heart lesions (39).

Inhaled NO has been assessed as a predictor of PA vasoreactivity in the cardiac catheterization laboratory and as a long-term therapeutic agent (40). The latter role has been limited by environmental concerns, difficulty in developing convenient delivery systems and potential toxicities. Despite these limitations, successful use of this agent for long-term therapy has been reported (41,42), and recent attempts have been made to modify the NO molecule to minimize toxicity as well as facilitate airway delivery (43). The other use of NO—as a vasodilator in the catheterization laboratory—has become increasingly popular. Recent studies have demonstrated its efficacy as a screening vasodilator agent and as a predictor of a safe response to oral vasodilators in PPH (44,45). An advantage of iNO is the avoidance of systemic hypotension, which can complicate testing with oral and intravenous agents. Nitric oxide reacts avidly with hemoglobin to yield the inactive metabolites nitrite and nitrate in the pulmonary circulation, thus preventing peripheral delivery of the inhaled agent (46).

Study objectives. We sought to evaluate the safety and efficacy of iNO as a pulmonary vasodilator in the cardiac catheterization laboratory in patients with both PPH and SPH. Because previous evaluations of NO in pulmonary hypertension mainly focused on the pediatric population, the 42 patients we studied is the largest adult population reported to date. Also unique to our study is the etiology of SPH. Intrinsic pulmonary disease was present in 71%, differing greatly from previous studies largely focusing on patients with congenital heart lesions.

Nitric oxide was extremely well tolerated by both groups, and no effect on systemic vascular tone was noted. Because NO is a highly volatile substance, side-chain reactions with oxygen can form toxic metabolites, including NO_2. Levels of NO_2 remained low throughout inhalation during our study.

All doses of NO used in this study (10, 20 and 40 ppm) significantly lowered the mean PA pressure in patients with pulmonary hypertension. Patients with higher RVEDP had less reduction of PA pressures. To our knowledge, this finding has not been described previously. Diastolic dys-

Table 4. Response of Patients With Primary and Secondary Pulmonary Hypertension to 40 ppm of NO Compared With Baseline Value

	Baseline	40 ppm NO	p Value
PPH Group			
Mean PAP (mm Hg)	51.5 ± 19.8	40.1 ± 18.9	<0.001
PVR (Wood U)	11.3 ± 8.2	8.1 ± 7.9	<0.001
Mean AoP (mm Hg)	105.2 ± 15.8	105.1 ± 15.6	0.940
SVR (Wood U)	24.0 ± 5.7	23.4 ± 7.8	0.504
Cardiac output (liters/min)	4.1 ± 1.1	4.4 ± 1.4	0.197
Aortic saturation (% oxygen)	91.2 ± 4.8	94.0 ± 4.0	0.014
PA saturation (% oxygen)	60.3 ± 10.4	64.9 ± 9.6	0.001
SPH Group			
Mean PAP (mm Hg)	42.8 ± 11.5	32.8 ± 10.3	<0.001
PVR (Wood U)	6.2 ± 3.8	4.5 ± 3.0	<0.001
Mean AoP (mm Hg)	103.2 ± 14.2	103.9 ± 16.9	0.766
SVR (Wood U)	20.8 ± 6.8	18.8 ± 5.7	0.033
Cardiac output (liters/min)	5.2 ± 1.8	5.3 ± 1.5	0.306
Aortic saturation (% oxygen)	92.4 ± 6.2	95.9 ± 2.9	0.009
PA saturation (% oxygen)	66.2 ± 10.6	71.7 ± 7.6	0.001

Data are presented as the mean value ± SD.
NO = nitric oxide; ppm = parts per million; other abbreviations as in Table 1.

function and right ventricular failure is likely a marker of long-standing pulmonary hypertension and may predict a population less likely to respond to vasodilators.

In our whole study group, the mean PA pressure and PVR significantly decreased during inhalation of NO. No effect on aortic pressure or SVR was seen, confirming the status of iNO as a selective pulmonary vasodilator. When classified by etiology, patients with SPH tended to be less ill than patients with PPH, with a better NYHA functional class (2.55 vs. 2.94), a higher cardiac output (5.15 vs. 4.12 liters/min) and lower PVR (6.2 vs. 11.3 Wood U). Despite these differences, the two groups responded to iNO at a similar rate (78% in PPH vs. 83% in SPH). In the PPH group, the majority of the drop in mean PA pressure occurred at the lowest dose of NO (10 ppm), with little additional diagnostic yield at higher doses. Similar results have been reported by Sitbon et al. (47). In contrast, the diagnostic yield was increased in patients with SPH at 20 and 40 ppm doses of NO. If only 10 ppm of NO was used as a screening test, 7 (29%) of 24 responders would have been missed, compared with only 2 (11%) of 18 responders in the PPH group.

Table 5. Response to Inhaled 100% Oxygen by Face Mask as Compared With 40 ppm of NO

	Baseline	100% Oxygen by FM	40 ppm NO
Mean PAP (mm Hg)	46.0 ± 11.6	42.1 ± 11.4	35.7 ± 11.1
		0.009	0.0002
PVR (Wood U)	8.0 ± 4.6	6.8 ± 3.7	5.7 ± 3.8
		0.003	0.0007
Aortic O_2 saturation (% oxygen)	90.8 ± 6.8	99.3 ± 1.5	95.4 ± 3.4
		0.0004	0.013
Responders		9/14 (64%)	11/14 (79%)

Data are presented as the mean value ± SD, with p values below (p values are in comparison to baseline values).
FM = face mask; NO = nitric oxide; O_2 = oxygen; PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance.

Mikhail et al. (48) previously measured venous and arterial blood levels of vasoactive mediators in patients with PPH and SPH; endothelin levels were found to be significantly elevated in both disorders. Compared with normal control subjects, patients with PPH had lower NO levels and patients with SPH had higher levels. This finding may help to explain the observed trend toward a greater response with higher doses of NO in SPH but no such effect in PPH.

Unexpected observations. The oxygen saturation in aortic and pulmonary blood significantly improved during NO inhalation in patients with SPH (92.4% to 95.9%, p = 0.0004 and 66.2% to 71.7%, p = 0.013, respectively). These results concur with previously published reports; also, improved oxygenation is a postulated benefit of iNO in this patient group (49). Because iNO is delivered preferentially to well-ventilated regions, the PAs supplying healthier lung beds dilate and may result in improved ventilation–perfusion matching.

To ensure that improved oxygenation was not, by itself, responsible for the vasodilatory effect of NO, the results of the 14 patients receiving both iNO and 100% oxygen by a non-rebreather face mask were reviewed. Although minimal changes in PVR and mean PA pressure (46 to 42.1 mm Hg) were seen with 100% oxygen, a larger drop in PVR and a significant drop in mean PA pressure (46 to 35.7 mm Hg, p = 0.02) was noted with 40 ppm of NO. Eleven (79%) of 14 patients were responders to NO, and 9 (64%) of 14 patients were responders to oxygen. If oxygen was used as the sole screening tool for pulmonary vasoreactivity, three responders would have been missed. One patient responding to oxygen would not have been identified using NO alone. As Atz et al. (16) recently postulated, a combination of NO and oxygen is likely to be the most sensitive screening test for pulmonary vasoreactivity.

Conclusions. This study confirms previous reports of the safety and pulmonary selectivity of NO in the cardiac catheterization laboratory for testing both patients with PPH and those with SPH. Patients with pulmonary hypertension appear to benefit hemodynamically from NO inhalation, regardless of their cause of pulmonary hypertension. Our data suggest that for SPH, a dose effect may be present, and use of higher doses may improve sensitivity of vasoreactivity screening. Concurrent testing with inhaled oxygen provides additional information.

Future directions. Nitric oxide has been shown to be useful in predicting a positive response to calcium channel blocking drugs in PPH. Positive responders to calcium channel blockers have survival benefit when treated long term with these agents (50). McLaughlin et al. (51) recently demonstrated that intravenous prostacyclin greatly improved hemodynamic data and functional class in patients with severely symptomatic SPH. Because this therapy is still limited by expense and generalized availability, an alternative approach should be sought. Inhaled and nebulized prostacyclin has shown recent promise and may be able to significantly reduce costs, as well as systemic complications related to other vasodilators (52–54). Several small trials have demonstrated that calcium channel blockers can lower pulmonary pressures in patients with chronic lung disease (55–57). This is important, as elevated pulmonary pressures have been shown to predict mortality in patients with chronic obstructive pulmonary disease (58). Galloe et al. (59) failed to see a benefit in terms of functional status or mortality when using isradipine in an unselected (no measurement of baseline pulmonary pressures or response to vasodilators) group of patients with chronic obstructive pulmonary disease. A large trial to study the effects of oral vasodilators in patients responding to iNO is necessary at this time.

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Reprint requests and correspondence: Dr. Thomas M. Bashore, Box 3012, Duke University Medical Center, Durham, North Carolina 27710. E-mail: thomas.bashore@duke.edu.

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