JACC Vol. 32, No. 4
October 1998:1068–73

Inhaled Nitric Oxide in Primary Pulmonary Hypertension

A Safe and Effective Agent for Predicting Response to Nifedipine

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Objectives. **The purpose of this study was to assess the utility of inhaled nitric oxide (NO), a selective pulmonary vasodilator, for predicting the safety and acute hemodynamic response to high-dose oral nifedipine in primary pulmonary hypertension (PPH).**

Background. **A significant decrease in pulmonary vascular resistance with an oral nifedipine challenge is predictive of an improved prognosis, and potential clinical efficacy in PPH. However, the required nifedipine trial carries significant first-dose risk of hypotension. While inhaled NO has been recommended for assessing pulmonary vasodilator reserve in PPH, it is not known whether it predicts the response to nifedipine.**

Methods. **Seventeen patients with PPH undergoing a nifedipine trial were assessed for hemodynamic response to inhaled NO at 80 parts per million for 5 minutes. The nifedipine trial consisted of 20 mg of nifedipine hourly for 8 hours unless limited by hypotension or intolerable side effects. Patients were classified as responders and nonresponders with positive response defined as ≥20% reduction in mean pulmonary artery pressure (mPA) or pulmonary vascular resistance (PVR) with the vasodilator administration.**

Results. **NO was safely administered to all participants. Seven of 17 (41.2%) responded to NO, and 8 of the 17 to nifedipine (47.1%). Nifedipine was safely administered in 14 of the 17. Three suffered either mild or severe hypotension, including one death. All NO responders also responded to nifedipine, and 9 of the 10 NO nonresponders were nifedipine nonresponders, representing a sensitivity of 87.5%, specificity of 100%, and overall predictive accuracy of 94%. All NO responders tolerated a full nifedipine trial without hypotension. There was a highly significant correlation between the effects of NO and nifedipine on PVR ($r = 0.67$, $p = 0.003$).**

Conclusions. **The pulmonary vascular response to inhaled NO accurately predicts the acute hemodynamic response to nifedipine in PPH, and a positive response to NO is associated with a safe nifedipine trial. In patients comparable with those evaluated, a trial of nifedipine in NO nonresponders appears unwarranted and potentially dangerous.**

(J Am Coll Cardiol 1998;32:1068–73)

Primary pulmonary hypertension (PPH) is a rapidly progressive and fatal disease (1). While no cure has been identified, anticoagulants (2,3), calcium channel blockers (3), and continuous infusion epoprostenol (4) have proven useful. The addition of epoprostenol to conventional therapy in patients with advanced symptoms improved 90-day survival, quality of life, and exercise capacity in Class III and IV patients (5). Despite the clear benefits of epoprostenol, there are patients for whom the risk of implanted catheter-related infection and cost will be excessive (e.g., those with less advanced symptoms and those who may derive benefit from calcium channel blocker therapy). Further, the availability of echo-Doppler for detecting pulmonary hypertension and heightened awareness of PPH related to dexfenfluramine (Redux) (6) make it likely more patients will be diagnosed at earlier stages. Until more effective oral agents become available, an important part of patient management will be selecting those for whom conventional therapy with calcium channel blockade is appropriate.

Because the long-term efficacy of nifedipine and diltiazem correlates with the acute response, the decision to use these agents has historically been based upon a hemodynamic trial. However, the invasive trials are labor intensive, require an intensive care unit (ICU) stay for 1–2 days, and have been associated with profound hypotension and death (7).

Acute hemodynamic trials with intravenous adenosine (7–12) and prostacyclin (13,14) have been used to evaluate pulmonary vascular vasodilator reserve in PPH, and as "screening vasodilators" for determining which patients may benefit from chronic oral calcium channel blocker therapy. Each is a nonselective vasodilator known to produce systemic side effects (11,13,14).

Nitric oxide (NO) is an endogenous endothelial–derived vasodilator mediated by vascular smooth muscle cell cGMP. When administered as an inhaled gas in patients with both primary and secondary forms of pulmonary hypertension, short-term NO selectively reduces both the mean pulmonary

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Manuscript received March 3, 1998; revised manuscript received May 29, 1998, accepted June 12, 1998.

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0735-1097/98/$19.00
PII S0735-1097(98)00361-1

Abbreviations and Acronyms

CO = cardiac output
mPA = mean pulmonary artery pressure
mRA = mean right atrial pressure
NO = nitric oxide
PPH = primary pulmonary hypertension
PVR = pulmonary vascular resistance

artery pressure (mPA) and pulmonary vascular resistance (PVR) with no side effects (15–18). While established as a selective pulmonary artery vasodilator and recommended as a suitable agent for pulmonary vasodilator testing, it is not known whether inhaled NO predicts the response to nifedipine.

We designed this study to evaluate the utility of inhaled NO for predicting the safety and pulmonary vascular response to a trial of high-dose oral nifedipine in PPH.

Methods

Seventeen patients with PPH (NIH criteria) scheduled to undergo an acute challenge with high-dose nifedipine to assess pulmonary vasodilator reserve also consented to a brief trial of inhaled NO. The study was approved by the Institutional Review Board of the University of Michigan. Patients with evidence for pulmonary veno-occlusive disease or systemic systolic pressure less than 90 mm Hg were excluded.

Hemodynamic assessment. Oral vasodilating drugs were held for 24 h. No sedation was used prior to or during the studies, and all trials were conducted in the fasting state. A radial or femoral artery 4 or 5 French catheter was inserted for pressure monitoring and blood gas analysis. A four-lumen balloon flotation catheter (optional use of a stiffening wire) was used for thermodilution cardiac output (CO), sampling of mixed venous oxygen saturation, and right heart pressures. The NO trial was conducted in the cardiac catheterization laboratory or coronary care unit (CCU), and the nifedipine trial the following morning in the CCU.

Thermodilution CO was defined as the average of the first two measurements if within 5%, or three within 10% agreement. Arterial and mixed venous blood samples were obtained at the time of thermodilution CO. The following pressures were obtained at 100 mm Hg scale and 50 mm/s paper speed and measured in mm Hg as the average during three respiratory cycles: mean right atrial (mRA); systolic and diastolic pulmonary artery; mean pulmonary capillary wedge (PCW); and systolic and diastolic systemic artery. Mean arterial (mBA or mFA) and mPA pressures were calculated using the average of one systolic and two diastolic divided by three. Systemic vascular resistance (SVR) and PVR were calculated as (mBA − mRA) ÷ CO and (mPA − PCW) ÷ CO, respectively, and expressed in absolute or Wood units.

Nitric oxide trial. Baseline measures for the NO trial were obtained on room air if the pO_2 was >60 mm Hg and arterial saturation >90%. Two patients required supplemental oxygen (FIO_2 24% and 28%) to maintain arterial saturation ≥92%. In three patients with right to left shunting at the atrial level (one atrial septal defect and two foramen ovale) the maximum arterial saturation was <92% on 28% FIO_2. NO was administered for 7 minutes at 80 parts per million (PPM) with a tight fitting mask, and data were collected in the last 2 minutes. The dose of NO and generation of nitrogen dioxide were measured using an NO delivery system (NOxBOX II; Bedfont Scientific) and NO analyzer (Sensormedics SensorNOx; Sensormedics BV).

Nifedipine trial. Patients were administered a constant infusion of 5% dextrose and 0.5 NaCL at 50–75 cc/h starting 8 hours prior and throughout the nifedipine trial. The nifedipine trial consisted of 20 mg of nifedipine given hourly for 8 hours unless limited by systemic hypotension (systolic pressure reduction greater than 20% accompanied by symptoms attributable to hypotension, or absolute value of less than 90 mm Hg) or intolerable side effects (19). The reference baseline was defined as the average over 4 hours preceding the first dose of nifedipine. All hemodynamic data were obtained in the recumbent position.

Response to vasodilator. Complications were a priori defined as major or minor. Major complications included hypotension requiring treatment, cardiogenic shock, or death. Minor complications were defined as symptoms requiring termination prior to completion of the dosing schedule.

Response to NO and nifedipine in comparison with baseline measures were calculated as absolute change and percent change, and expressed as responders or nonresponders. Although not uniformly established in the literature (7,11,12,19), responders were defined a priori as those with a decrease in mean pulmonary artery pressure (mPA) or pulmonary vascular resistance of ≥20% (12) without significant systemic hypotension. Those who developed severe systemic hypotension, for whom significant hemodynamic assessment was not possible, were assigned mPA and PVR reduction of 0% (i.e., fixed pulmonary vascular response to vasodilation).

Statistical analysis. Sensitivity, specificity, predictive value, and predictive accuracy were calculated using true positive and true negative results defined as identifying nifedipine responders and nonresponders, respectively. Between group comparisons were made by the Student *t* test. Pearson correlation coefficient was used to compare nifedipine and NO responses. Linear regression modeling was used to test the predictability of nifedipine response by NO and hemodynamic measures.

Results

Patient population. All 17 patients completed both trials. The average age of participants was 47.5 ± 14 years; 88% were women. The majority of patients were obese (body mass index [BMI] >27.5 kg/M^2). The mean weight was 81.1 ± 20 kg, height 1.7 ± 0.1 M, and BMI 29.6 ± 5.3 kg/M^2. Three patients were NYHA functional Class II, 11 Class III, and three Class IV. The study population probability for 1-year survival based

Table 1. Study Population

Demographic Data		Hemodynamic Data	
No. of patients	17	RA	11.4 ± 7.0 mm Hg
Age	45 ± 14 years	sPA	92 ± 19 mm Hg
Female	88.2%	dPA	40 ± 10 mm Hg
BSA	1.9 ± 0.3 kg/m^2	mPA	57.5 ± 12.4 mm Hg
NYHA Class	3 ± 0.6	PCWP	12.4 ± 3.0 mm Hg
Est. 1-year survival	67.5 ± 16.4%	sBA	130 ± 21 mm Hg
		dBA	75 ± 13 mm Hg
		mBA	88.5 ± 14.1 mm Hg
		CO	4.6 ± 1.6 L/min
		art O_2 sat	91.9 ± 7%
		MVO_2	63.9 ± 10%
		PVR	11.2 ± 5.4 Wood Units

Baseline patient demographic and hemodynamic data. s = systolic; d = diastolic; m = mean; RA = right atrium; BA = brachial artery; PA = pulmonary artery; CO = cardiac output; PCWP = pulmonary artery occlusive pressure; MVO_2 = mixed venous oxygen; BSA = weight (kg)/height (m^2); Est. 1-year survival as calculate using NIH registry formula (20); RA = mean right atrial pressure; PA(s/d) = pulmonary artery pressure systolic over diastolic; mPA = mean pulmonary artery pressure; PCWP = mean pulmonary capillary wedge pressure; BP = systemic blood pressure; mBA = mean systemic pressure; CO = cardiac output by thermodilution, art O_2 sat = arterial oxygen saturation by blood gas analysis; MVO_2 = mixed venous oxygen saturation by blood gas analysis; PVR = pulmonary vascular resistance ([mPA-wedge pressure]/CO).

on the NIH registry formula, which incorporates RA pressure, mPA pressure, and CO (20), was 67.5 ± 16%. Baseline mRA was 11.0 ± 7 mm Hg, mPA 57.5 ± 12 mm Hg, CO 4.7 ± 2 L/m, PVR 11.5 ± 6 Wood units, mBA 92.8 ± 14 mm Hg, systemic O_2 saturation 92 ± 7%, and mixed venous saturation (MVO2) 64 ± 10% (Table 1). Arterial saturation was less than 85% in two patients; one with a low-affinity hemoglobin (hemoglobin Washtenaw, patient #8), and one an atrial septal defect with bi-directional shunting (patient #17).

NO response. NO was administered without side effects in all 17 patients. Three patients had mild transient arterial desaturation (to 88%). NO administration resulted in a mean reduction in mPA pressure from 57.5 ± 12.4 to 54.0 ± 12.8 mm Hg (6.3 ± 9.3%, p = NS), and mean reduction in PVR from 11.2 ± 5.4 to 10.2 ± 5.8 Wood units (11.4 ± 19.1%, p = NS). Additionally, there was no significant change in heart rate, mean systemic blood pressure, arterial saturation, mixed venous saturation, pulmonary capillary wedge pressure, or cardiac output. NO response is summarized in Table 2.

Seven of the 17 patients (41.2%) were NO responsive. The mean percent reduction in mPA in NO responders and nonresponders was 12.3 ± 8.9% and 2.2 ± 7%, respectively (p = 0.03). The mean percent reduction in PVR was 29.3 ± 11.0% and −1.2 ± 12.1% for NO responders and nonresponders, respectively (p = 0.00007).

Nifedipine response. Nifedipine was administered safely in 14 of the 17 patients. Two patients experienced first-dose severe hypotension and shock (one death, one successfully treated), and one had mild hypotension. Those with hemodynamic instability could not undergo complete hemodynamic assessment and were assigned mPA and PVR reduction of 0% (i.e., fixed pulmonary hypertension). The mean nifedipine dose was 129.4 ± 52 mg. Nifedipine administration resulted in a reduction in mPA from 59.1 ± 11.1 to 53.4 ± 11.0 mm Hg (8.0 ± 10%, p = NS), and reduction in PVR from 12.6 ± 6.1 to 9.3 ± 5.1 Wood units (19.7 ± 13%, p = NS). The mean systemic blood pressure, in those without severe hypotension, fell from 92.5 ± 15.3 to 74.8 ± 12.9 mm Hg (p = 0.001). There was no significant change in heart rate, arterial saturation, mixed venous saturation, pulmonary capillary wedge pressure, or CO. Nifedipine response is summarized in Table 2.

Of the 17 patients, 8 (47.1%) were nifedipine responders. The mean percent reduction in mPA in responders and nonresponders was 11.3 ± 11% and 2.8 ± 7.8%, respectively (p = 0.09). The mean percent reduction in PVR was 28.6 ± 10% and 10.2 ± 8% for responders and nonresponder, respectively (p = 0.02).

Comparison of NO and nifedipine response. All seven of the NO responders responded to nifedipine and nine of the 10 NO nonresponders were nifedipine nonresponders. NO predicted the response to nifedipine with a sensitivity of 87.5%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 94%. The overall predictive accuracy of NO was 94%. All NO responders tolerated nifedipine without hypotension.

The percent change in PVR with the two vasodilators was normally distributed. There was a significant correlation between the effects of NO and nifedipine on PVR (Pearson's r = 0.67, p = 0.003, (Fig. 1). Linear regression analysis showed NO to predict nifedipine response independent of mRA, mPA pressure, and CO. No hemodynamic measure, alone or in combination, was predictive of response to nifedipine.

Discussion

The mean survival in PPH from symptom onset is approximately 3 years (21). Patients generally present with progressive exertional dyspnea, fatigue, and chest pressure and ultimately develop severe hypoxemia and death due to hypotension and low output or a fatal ventricular arrhythmia. The outcome has, to varying degrees, been favorably impacted by four treatment modalities; anticoagulation (2,3), oral calcium channel blocking drugs (3), continuous infusion epoprostenol (4), and lung transplantation (22).

Continuous infusion of intravenous epoprostenol appears to change the natural history of PPH, and has been approved for use in the United States for patients with moderate to severe symptoms (NYHA Class III and IV). When added to conventional treatment (66% of whom were an oral vasodilator therapy), epoprostenol has been shown to reduce mortality and symptoms, and delay the need for lung transplantation (5).

The expense and necessity for an indwelling catheter and infusion pump make epoprostenol less than an ideal agent, particularly in those without severe limitation. Subgroups of patients in whom oral calcium channel blocker therapy may be effective include those with mild to moderate symptoms and moderately increased pulmonary vascular resistance, and pos-

Table 2. Hemodynamic Measures On Individual Patients Before and After NO and Nifedpine

		Systemic BP (mm Hg)								CO (L/min)				PCWP				PA Pressure (mm Hg)									Pulm Vasc Resistance (Wood units)					
Patient #	Response	Pre NO(s/d)	mean	Post NO(s/d)	mean	Pre Nif(s/d)	mean	Post Nif(s/d)	mean	Pre NO	Post NO	Pre NIf	Post Nif	Pre NO	Post NO	Pre Nif	Post Nif	Pre NO(s/d)	mean	Post NO(s/d)	mean	% Red	Pre Nif	mean	Post Nif	mean	% Red	Pre NO	Post NO	% Red	Pre Nif	Post Nif	% Red
1	NO+Nif+	115/83	94	123/81	98	136/95	109	88/73	78	5.7	6.9	4.4	3.5	12	18	12	18	56/36	43	54/32	39	9.3	64/26	39	56/24	35	10.3	5.4	3.0	44.1	6.1	4.9	20.8
2	NO+Nif+	100/47	68	99/50	66	100/47	71	99/50	67	4.8	4.8	3.6	4.9	12	12	15	12	70/23	39	54/19	31	20.5	88/34	52	60/28	39	25.0	5.6	4.0	29.6	10.3	5.5	46.3
3	NO+Nif+	146/77	100	150/82	105	123/59	80	115/55	75	4.9	5.1	4.8	4.9	10	12	11	9	68/30	43	63/27	39	9.3	76/28	44	62/22	35	20.4	6.7	5.3	21.3	7.0	5.2	25.1
4	NO+Nif+	132/72	92	133/70	92	117/61	80	114/58	77	5.4	6.3	3.8	4.8	10	12	11	12	73/32	46	54/26	35	23.9	70/30	43	72/30	44	−2.3	6.7	3.7	45.2	8.4	6.7	20.9
5	NO+Nif+	146/72	97	147/72	97	149/67	94	124/61	82	3.4	4.2	4.2	5.0	13	14	15	15	93/28	50	94/28	50	0	108/30	56	100/27	51	8.9	10.9	8.6	21.2	9.8	7.2	26.2
6	NO+Nif+	141/78	99	145/80	102	144/78	101	120/57	78	5.8	6.9	4.8	5.3	10	10	10	9	106/50	69	105/47	66	4.3	108/55	73	99/45	63	13.7	10.2	8.1	20.6	13.1	10.1	22.9
7	NO+Nif+	128/95	108	134/91	105	144/71	95	120/55	77	2.4	2.9	2.7	3.5	14	14	12	12	115/42	66	96/33	54	18.2	126/55	79	105/40	62	21.5	21.7	13.8	36.4	24.8	14.3	42.4
8	NO−Nif−	108/66	80	112/71	88	104/66	79	93/63	73	4.4	4.3	3.6	3.8	10	11	18	20	100/45	63	101/43	62	1.6	100/56	67	100/44	63	6.0	12.1	11.9	1.6	13.6	11.3	16.8
9	NO−Nif−	117/85	96	116/87	97	127/96	106	109/86	94	2.3	2.3	1.7	1.8	12	12	20	20	95/50	65	92/52	65	0	92/44	60	96/44	61	−1.7	23.1	23.1	0	23.6	22.8	3.2
10	NO−Nif−	110/59	76	109/56	74	116/58	72	113/53	73	4.7	4.3	4.7	4.7	10	10	10	10	84/30	48	80/31	47	2.1	90/36	54	88/36	53	1.8	8.1	8.6	−6.3	9.4	9.2	2.3
11*	NO−Nif−	122/77	92	144/88	107	126/83	97	*	*	3.0	2.5	3.0	*	12	14	12	*	88/39	55	90/44	59	−7.3	92/45	61	*	*	*	14.4	18.0	−25.5	16.3	*	*
12	NO−Nif−	130/63	85	130/64	86	134/71	92	132/68	89	8.0	7.2	11.0	10.3	17	19	15	16	86/33	51	95/35	55	−7.8	100/36	57	96/32	53	7.0	4.3	5.0	−17.6	3.8	3.6	5.9
13	NO−Nif−	113/85	94	114/64	81	113/60	78	96/51	66	3.6	3.9	3.2	3.8	11	10	12	12	102/42	62	116/38	64	−3.2	110/35	60	114/40	65	−8.3	14.2	13.9	2.2	15.0	14.0	7.0
14*	NO−Nif−	110/72	88	113/76	88	125/78	94	*	*	2.4	2.4	2.2	*	23	26	22	*	108/56	73	112/52	72	1.4	102/56	71	*	*	*	20.9	19.2	8.0	22.3	*	*
15	NO−Nif−	178/96	123	166/90	115	184/102	131	110/64	80	6.7	6.5	7.0	6.7	12	12	12	12	130/60	83	120/50	73	12.0	120/48	72	100/44	63	12.5	10.6	9.4	11.3	8.6	7.6	11.6
16*	NO−Nif−	154/64	92	153/64	93	154/64	91	*	38	4.4	3.9	4.0	*	10	10	9	*	86/32	53	78/26	47	11.3	98/41	60	*	*	*	9.8	9.5	3.1	12.6	*	*
17	NO−Nif+	159/90	113	147/91	108	131/89	103	120/78	92	6.0	5.3	4.9	6.9	13	15	8	8	102/48	69	89/43	60	13.0	96/36	56	100/40	60	−7.1	9.3	8.4	9.7	9.8	7.5	23.5
	AVG	130/75	88.5	131/75	94.2	131/73	92.5	111/62	75.9	4.6	4.7	4.3	5.0	12.4	13.6	13.1	13.3	92/40	57.5	88/37	54.0	6.4	96/41	59.1	89/33	36.3	7.7	11.4	10.2	12.1	12.6	9.3	19.6
	SD		14.1		12.8		15.3		13.2	1.6	1.6	2.1	2.0	3.3	4.2	3.8	3.9		12.4		12.8	9.3		11.1		2.3	10.5	5.8	5.8	19.9	6.1	5.1	13.4

Symbols + and − signify positive and negative vasodilator response, respectively. *Those with nifedipine hypotension whose measures were not obtainable. % Red = percent reduction with vasodilator. A negative value signifies an increase. Mean and standard deviations (SD) are recorded at the bottom.

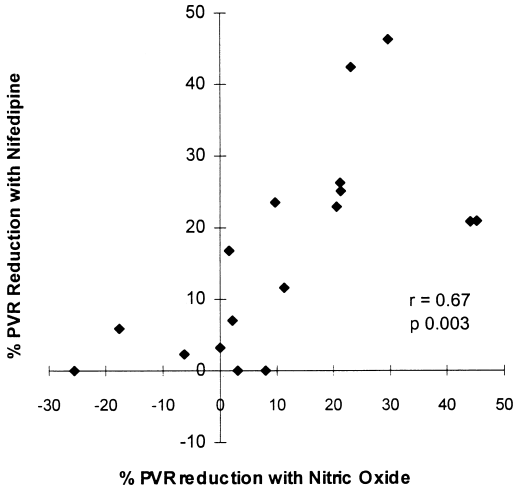

Figure 1. A plot of the reduction in pulmonary vascular resistance (PVR) with NO and nifedipine is shown. The three patients with nifedipine hypotension were assigned PVR reduction of 0% (i.e., fixed PVR).

sibly those with Class III symptoms with good pulmonary vasodilator reserve (a subset of patients not separately identified in the epoprostenol trials) (1,3,5).

Nifedipine trial safety. Only 25% of PPH patients have a favorable hemodynamic response and symptomatic benefit from calcium channel blocking agents, and there is a significant risk in their administration (3,19). The nonselective vasodilation and negative inotropy associated with calcium blockade may result in fatal or near fatal systemic hypotension. While several hemodynamic parameters (markedly elevated mRA, mPA, and depressed CO) may identify a group at risk for adverse effects, the evaluation of pulmonary vascular reserve prior to nifedipine challenge has become standard of care (7). The use of short-acting intravenous vasodilators to select patients for a trial with calcium channel blockers has been recommended, but no agents have been approved for such use (1).

Predicting nifedipine response with adenosine. The response to intravenous adenosine has been shown to correlate with that of nifedipine. In the largest reported trial of adenosine use in PPH (15 patients), Schrader et al. (11) found adenosine response to reasonably predict response to nifedipine. However, two of 12 adenosine responders had hypotension with nifedipine administration, suggesting that demonstration of pulmonary vasodilator reserve with adenosine does not predict a safe nifedipine trial. A second study reported that a subgroup of adenosine responders developed systemic hypotension with nifedipine (23). This may be a function of differing dose response, broader pulmonary vascular effects with adenosine than nifedipine, or possibly greater negative inotropic effects of nifedipine on right and left ventricular function.

Predicting nifedipine response with prostacyclin. The acute hemodynamic response to prostacyclin also correlates reasonably well with the initial hemodynamic response to nifedipine, and has been used to select patients for nifedipine trials (14). Additionally, prostacyclin responders have a better long-term response to nifedipine than nonresponders. The response to intravenous PGI_2, available as epoprostenol, has been recommended as an equivalent alternative to adenosine for selecting patients for an oral calcium channel blocker trial (1). However, the sensitivity and specificity of predicting nifedipine response with prostacyclin testing is not known.

Nitric oxide. Inhaled NO selectively dilates the pulmonary vasculature, has minimal systemic side effects, and with the aid of a respiratory therapist is easily administered. Continuous NO has been safely administered for days in children with pulmonary hypertension (24,25), adults with respiratory distress syndromes (26), and as bridge to lung transplantation (27). Because of a very short half life measurable in seconds, it is particularly useful as a testing agent. Prolonged use at high doses (especially in ventilated patients on high flow oxygen) may result in the accumulation of toxic byproducts; namely nitric dioxide (NO_2) (28–30). Accurate simple tools for measuring the concentration of inhaled NO and NO_2 are readily available. Given these favorable properties, NO has been recommended as a suitable agent for acute pulmonary vasodilator testing. Unlike adenosine and epoprostenol though, NO has not previously been shown to predict nifedipine response.

This study was designed to test whether NO could predict the safety and short-term efficacy of nifedipine in PPH. The long-term outcome in the NO and nifedipine responders was not evaluated in this study, as all nonresponders were treated with continuous infusion epoprostenol (thus confounding patient outcomes). Pulmonary vasodilator response to 5 minutes of 80 PPM of inhaled NO was compared with the hourly administration of 20 mg of nifedipine to a maximum of eight doses or intolerance. NO was administered without untoward effects in all patients, and all NO responders underwent a safe nifedipine trial. NO accurately predicted nifedipine response in 94%. Only one patient was misclassified with NO.

Conclusions. The pulmonary vascular response to inhaled NO accurately predicts the acute hemodynamic response to nifedipine in PPH, and should be considered as a safe alternative to adenosine and prostacyclin for vasodilator testing. In patients comparable with those evaluated herein, a trial of nifedipine in NO nonresponders with severely elevated PVR appears unwarranted and potentially dangerous. When compared with published reports on adenosine in PPH, NO responders would appear to have a higher likelihood of a safe nifedipine trial with comparable or better predictive value of nifedipine response. Ongoing studies with larger numbers of patients will address whether, as this study suggests, a favorable acute response to NO ensures a safe trial with nifedipine. Whether the initial response to inhaled NO is predictive of the long-term efficacy of calcium channel blockade awaits further study.

We gratefully acknowledge Sherrie Howie, RN, and the University of Michigan Internal Medicine housestaff who assisted in patient care, and Nancy Field for manuscript preparation.

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