Research Article

Vasoreactivity to inhaled nitric oxide with oxygen predicts long-term survival in pulmonary arterial hypertension

Rajeev Malhotra[1], Dean Hess[2,3], Gregory D. Lewis[1], Kenneth D. Bloch[1,3], Aaron B. Waxman[4], and Marc J. Semigran[1]

[1]Department of Medicine, Cardiovascular Research Center and Cardiology Division, Massachusetts General Hospital and Harvard Medical School, Boston, [2]Respiratory Care Services, Massachusetts General Hospital, Boston, [3]Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, [4]Pulmonary Critical Care Medicine and Cardiovascular Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA

ABSTRACT

Pulmonary vasodilator testing is currently used to guide management of patients with pulmonary arterial hypertension (PAH). However, the utility of the pulmonary vascular response to inhaled nitric oxide (NO) and oxygen in predicting survival has not been established. Eighty patients with WHO Group I PAH underwent vasodilator testing with inhaled NO (80 ppm with 90% O_2 for 10 minutes) at the time of diagnosis. Changes in right atrial (RA) pressure, mean pulmonary artery pressure (mPAP), pulmonary capillary wedge pressure, Fick cardiac output, and pulmonary vascular resistance (PVR) were tested for associations to long-term survival (median follow-up 2.4 years). Five-year survival was 56%. Baseline PVR (mean±SD 850±580 dyne-sec/cm^5) and mPAP (49±14 mmHg) did not predict survival, whereas the change in either PVR or mPAP while breathing NO and O_2 was predictive. Patients with a ≥30% reduction in PVR with inhaled NO and O_2 had a 53% relative reduction in mortality (Cox hazard ratio 0.47, 95% confidence interval (CI) 0.23-0.99, P=0.047), and those with a ≥12% reduction in mPAP with inhaled NO and O_2 had a 55% relative reduction in mortality (hazard ratio 0.45, 95% CI 0.22-0.96, P=0.038). The same vasoreactive thresholds predicted survival in the subset of patients who never were treated with calcium channel antagonists (n=66). Multivariate analysis showed that decreases in PVR and mPAP with inhaled NO and O_2 were independent predictors of survival. Reduction in PVR or mPAP during short-term administration of inhaled NO and O_2 predicts survival in PAH patients.

Key Words: pulmonary arterial hypertension, vasodilator testing, nitric oxide, vasoreactivity

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a disease characterized by elevated pulmonary arterial pressures and progressive right ventricular dysfunction.[1,2] Right heart catheterization (RHC) with pulmonary vasodilator testing is recommended both to establish the diagnosis of PAH and to enable selection of appropriate medical therapy.[3,4] Vasodilators with a short duration of action, such as inhaled nitric oxide (NO), are preferred for vasodilator testing.[4] A decrease in mean pulmonary artery pressure (mPAP) by ≥10 mmHg to an absolute level of <40 mmHg without a decrease in cardiac output (CO) is defined as a positive pulmonary vasodilator response,[3-6] and responders are considered for long-term treatment with calcium channel antagonists (CCA).[7-9] Less than 15% of idiopathic PAH (IPAH) patients are deemed responders during testing, and even fewer exhibit long-term responsiveness to CCA.[8]

It is unknown whether acute pulmonary vasodilator testing with inhaled NO and O_2 can be used to predict

Address correspondence to:
Dr. Marc J. Semigran
Division of Cardiology, Massachusetts General Hospital
GRB 800, 55 Fruit Street
Boston MA 02114 USA
Phone: 617-726-8862
Fax: 617-726-4105
Email: msemigran@ partners.org

Access this article online	
Quick Response Code:	Website: www.pulmonarycirculation.org
	DOI: 10.4103/2045-8932.83449
	How to cite this article: Malhotra R, Hess D, Lewis GD, Bloch KD, Waxman AB, Semigran MJ. Vasoreactivity to inhaled nitric oxide with oxygen predicts long-term survival in pulmonary arterial hypertension. Pulm Circ 2011;1:250-8.

outcomes in PAH patients, particularly in those not treated with CCA.[4] In this study, we investigated the ability of pulmonary vasodilator testing with inhaled NO and O_2 in PAH to add to previously described predictors of clinical outcomes.[10,11] We observed that the ability of inhaled NO and O_2 to reduce PVR and mPAP each predict improved survival.

MATERIALS AND METHODS

Patient sample and data collection

All adult patients from the Massachusetts General Hospital Pulmonary Hypertension Center registry were included in this retrospective study if they (1) met criteria for PAH[2] defined as a mPAP >25 mmHg at rest and a PCWP ≤15 mmHg with a PVR greater than 240 dynes-sec/cm^5 and (2) if they underwent acute vasodilator testing with inhaled NO and O_2 at the time of diagnosis and prior to the initiation of PAH-specific therapy during the years 2001-2008. Fifteen patients with PAH who underwent vasodilator testing were excluded from analysis because of concurrent PAH-specific treatment. Patients with IPAH, familial PAH, or PAH associated (APAH) with connective tissue disease, portal hypertension, congenital systemic pulmonary shunts, human immunodeficiency virus (HIV), anorexigen use, or genetic disorders such as Gaucher's disease were included. Patients underwent evaluation for and were excluded from the study if diagnosed with a World Health Organization (WHO) non-Group I etiology for their pulmonary hypertension, including chronic thromboembolic pulmonary hypertension.[4] Baseline demographic and clinical data was collected including age, gender, ethnicity, presence of related co-morbid conditions, WHO functional class, six-minute walk distance, diffusion capacity with carbon monoxide (DLCO), serum creatinine levels, and left ventricular ejection fraction (LVEF). Pharmacologic therapies for PAH were subsequently initiated at the discretion of the responsible physician. Fifty-five patients underwent vasodilator challenge from 2004-2008 and only patients that had a vasodilator response to inhaled NO and O_2 by the current definition (≥10 mmHg decrease to less than 40 mmHg without a decrease in CO) were considered for CCA therapy.[5,12] Prior to this time, the decision to administer CCA therapy was made based on an earlier definition of a vasoreactive response: 20% reduction in both PVR and mPAP with inhaled NO and O_2.[9] Patients who exhibited this response were placed on chronic CCA therapy only if they subsequently had a favorable response to acute administration of high doses of CCA.[7] Survival data was obtained both from hospital records and the Social Security Death Index (http://ssdi.rootsweb.ancestry.com/). A retrospective analysis of factors predicting survival was performed. This protocol was approved by the Partners Institutional Review Committee (#2010P000308).

Acute pulmonary vasodilator testing

As part of standard practice, patients underwent placement of a pulmonary artery catheter with fluoroscopic guidance after obtaining informed consent. Baseline measurements obtained in patients while breathing room air included right atrial (RA) pressure, PAP, pulmonary capillary wedge pressure (PCWP), arterial oxygen saturation and partial pressure, mixed venous oxygen saturation and partial pressure, and hemoglobin concentration. An MRM-2 VO_2 meter (Waters Associates, Rochester, Minn.) was used to obtain oxygen consumption. Measurements were repeated while patients were breathing 90% oxygen supplemented with 80 parts per million (ppm) NO for 10 minutes via facemask using an INOvent delivery system (Ikaria, Clinton, NJ). NO and NO_2 concentrations and FiO_2 were monitored continuously at the inlet of the facemask. The flow rate of NO gas mixed with O_2 was adjusted to maintain NO_2 concentrations below 2 ppm. Fick CO was calculated, using both the oxygen bound to hemoglobin as well as the dissolved oxygen in each blood sample. PVR was subsequently calculated as (mPAP–PCWP)/CO and was expressed in dynes-sec/cm^5. In patients with congenital heart disease, pulmonary blood flow was utilized to calculate PVR. Cardiac index was calculated as the CO/(body surface area) and expressed in L/min/m^2.

Statistical analyses

Statistical tests were performed using the STATA 8.0 software package (StataCorp LP, College Station, Tex.). Normality of data was assessed using the Shapiro-Wilk test. Continuous variables are expressed as mean±SD or median (interquartile range, IQR). Group baseline characteristics were compared using either the Student t test, Mann-Whitney U statistic, or Fisher's exact test, as appropriate. Survival was determined starting from the day of acute pulmonary vasodilator challenge to the time of data collection. The Kaplan-Meier method was utilized to estimate the proportion of patients surviving at a given time point, and survival curves were compared using the log rank test. Age-adjusted and multivariate Cox proportional hazard ratio modeling was utilized to determine significant hemodynamic predictors of survival. Percent changes in PVR and mPAP induced by vasodilator challenge were analyzed both as continuous variables and dichotomous variables stratified by the median change. Correlation analysis was performed using a generalized linear model of regression. Forest plots for subgroup analysis were generated using GraphPad Prism 5.0 (GraphPad Software, La Jolla, Calif.). P-values were considered significant if ≤0.05.

RESULTS

Baseline characteristics

A total of 80 patients with PAH were evaluated with inhaled NO and O_2 vasodilator testing at the time of diagnosis and had a median follow-up time of 2.4 years (IQR 1.0, 4.6). Baseline clinical characteristics and values of hemodynamic parameters are provided in Table 1. The PAH patients had a mean age of 55±17 years, a baseline mPAP of 49±14 mmHg, and a PVR of 850±580 dynes-sec/cm^5. After vasodilator testing, patients were initiated on therapy for PAH including prostanoids (44%), phosphodiesterase 5 (PDE5) inhibitors (46%), endothelin receptor antagonists (ETA, 26%), CCA (18%), and warfarin (53%). Fourteen total patients were treated with CCA, 5 of whom met the current criteria for a vasoreactive response, 5 who met the criteria preceding 2004, and 4 patients who were started on CCA for other indications (3 with diltiazem for atrial fibrillation, 1 with amlodipine for systemic hypertension).

Pulmonary vasoreactivity to inhaled NO and O_2 predicts survival

At 5 years, Kaplan-Meier survival for the overall population was 56%. Cox proportional hazard modeling identified age (hazard ratio (HR) 1.63 for every decade of age, 95% confidence interval (CI) 1.27-2.09, P<0.001), RA pressure >10 mmHg (HR 2.90, 95% CI 1.40-6.01, P=0.004), the presence of portopulmonary hypertension (Cox HR 2.89, 95% CI 1.37-6.12, P=0.005), renal dysfunction (Cox HR 1.21 for every 10 mL/min/1.73 m^2 decrease in Modified Diet in Renal Disease (MDRD) creatinine clearance, 95% CI 1.06-1.39, P=0.005), and a reduced DLCO (Cox HR 1.34 for every 10% decrease, 95% CI 1.09-1.65, P=0.006) as univariate predictors of mortality. In addition, we identified that the percent decrease in PVR (ΔPVR) or mPAP (ΔmPAP) with inhaled NO and O_2 from baseline predicted long-term survival in PAH patients both in univariate (Figs. 1 and 2) and age-adjusted multivariate analyses (Table 2). For every 10% reduction in baseline PVR with vasodilator, there was a reduction in age-adjusted mortality by a ratio of 0.82 (95% CI 0.69-0.98, P=0.025), while every 10% reduction in baseline mPAP with vasodilator reduced mortality by a factor of 0.60 (95% CI 0.43-0.83, P=0.002). Acute changes in PVR and mPAP in response to breathing inhaled NO and O_2 were also able to predict survival after adjusting for multivariate predictors that included age, RA pressure, DLCO, and the presence of portopulmonary hypertension (Table 2). Baseline mPAP, PVR, and cardiac index were not predictors of survival. In univariate analysis, WHO Functional Class III and IV (versus Class I and II combined) exhibited a trend towards predicting mortality (Cox HR 2.05, 95% CI 0.88-4.79, P=0.096). The 7 patients (9%) demonstrating vasodilator responsiveness defined by current guideline criteria (decrease in mPAP by at least 10 mmHg to <40

Table 1: Patient baseline characteristics

	PAH patients (*n*=80)	Surviving patients (*n*=49)	Non-surviving patients (*n*=31)
Age at RHC (years)	55±17	50±17	62±14†
Gender - Female (%)	57 (71)	38 (78)	19 (61)
Ethnicity (%)			
Caucasian	65 (81)	38	27
Black	6 (8)	5	1
Hispanic	5 (6)	3	2
Asian	3 (4)	3	0
Native American	1 (1)	0	1
Diagnosis (%)			
Idiopathic PAH	21 (26)	15	6
Familial PAH	7 (9)	4	3
Collagen vascular disease	23 (29)	15	8
Portal hypertension (%)	16 (20)	5	11†
Congenital heart disease	7 (9)	5	2
HIV-associated	3 (4)	3	0
Anorexigen	2 (3)	1	1
Gaucher's disease	1 (1)	1	0
Functional parameters			
WHO functional class I/II/III-IV	4/22/54 (5/28/68)	3/16/30	1/6/24
Six-minute walk distance (m)*	350±160	370±160	280±160
Hemodynamic parameters			
RA pressure (mmHg)	10±6	9±5	12±6†
PVR (dynes-sec/cm^5)	850±580	870±650	820±450
Mean PAP (mmHg)	49±14	48±16	51±11
Systolic PAP (mmHg)	78±23	76±24	81±21
Diastolic PAP (mmHg)	29±11	30±12	28±10
Cardiac index (L/min/m^2)	2.6±0.9	2.6±0.9	2.6±1.0
PCWP (mmHg)	10±4	10±3	10±4
LVEF (%)	68±8	69±9	68±12
DLCO (%)	61±21	67±20	51±21†
Hemoglobin (g/dL)	13.2±2.2	13.4±2.1	12.8±2.3
MDRD Creatinine clearanceΔ	75 (57,99)	76 (61,102)	73 (52,93)

Values are presented as mean+SD, median (IQR), or n (%).
*n=24. †P<0.05, comparing surviving patients to non-surviving patients with either the student *t* test, the Mann-Whitney U statistic, or Fisher's exact test, as appropriate.
Δ in ml/min/1.73 m^2

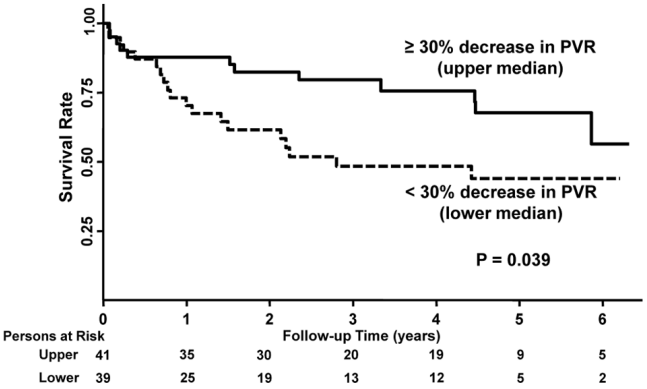


Figure 1: Changes in PVR with inhaled NO and O_2 predict survival in PAH. Kaplan-Meier survival curves for PAH patients stratified by vasoreactivity, defined by at least a 30% decrease in PVR with vasodilator challenge. The Log-rank test shows reduced mortality in vasoreactive patients (P=0.039).

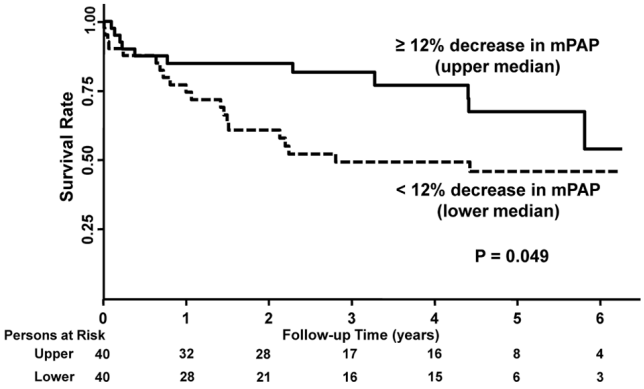


Figure 2: Changes in mPAP with inhaled NO predict and O_2 survival in PAH. Kaplan-Meier survival curves for PAH patients stratified by vasoreactivity, defined by at least a 12% decrease in mPAP with vasodilator challenge. The Log-rank test demonstrates reduced mortality in vasoreactive patients (P=0.049).

Table 2: Hemodynamic predictors of long-term survival

Variable	Adjusted for age		Adjusted for age and other multivariate predictors†	
	Cox HR (95% CI)	P-value	Cox HR (95% CI)	*P*-value
Baseline parameters				
Right atrial pressure >10 mmHg (n=30) versus≤10 mmHg (n=50)	2.14 (1.03-4.44)	0.04	–	–
PVR (dynes-sec/cm^5)	0.98 (0.93-1.05)	0.62	0.96 (0.87-1.06)	0.39
mPAP (mmHg)	1.00 (0.98-1.03)	0.75	1.00 (0.96-1.04)	0.91
Cardiac index (L/min/m^2)	1.37 (0.90-2.10)	0.15	1.19 (0.67-2.13)	0.55
Vasoreactivity parameters (continuous)				
ΔPVR in response to iNO (for every 10% decrease)	0.82 (0.69-0.98)	0.025	0.60 (0.44-0.80)	0.001
ΔmPAP in response to iNO (for every 10% decrease)	0.60 (0.43-0.83)	0.002	0.42 (0.25-0.71)	0.001
Vasoreactivity parameters (dichotomous)				
Vaso-responsive to iNO by guidelines[4]	0.66 (0.16-2.80)	0.57	0.72 (0.14-3.73)	0.69
ΔPVR≥30% (vs.<30%) in response to iNO*	0.47 (0.23-0.99)	0.047	0.17 (0.06-0.54)	0.002
ΔmPAP≥12% (vs.<12%) in response to iNO*	0.45 (0.22-0.96)	0.038	0.19 (0.06-0.57)	0.003

Variables are treated as either continuous or dichotomous, as indicated. iNO, inhaled nitric oxide and O_2. ΔPVR, decrease in PVR. ΔmPAP, decrease in mPAP. *Grouped into upper versus lower median. †Adjusted for age, RA pressure, presence of portopulmonary hypertension, and DLCO

mmHg without a decrease in CO)[4] had a hazard ratio for mortality of 0.66 compared to the remaining 73 patients (95% CI 0.16-2.80).

The median reduction in PVR with inhaled NO and O_2 was 30% (IQR 15%, 50%), while the median reduction in mPAP was 12% (IQR 4%, 21%). These medians were used to define vasoreactive and non-vasoreactive subgroups. Characteristics of the population stratified above and below the median for both ΔPVR and ΔmPAP are presented in Table 3. There were no differences in age, gender, WHO functional classification, six-minute walk distance, or baseline hemodynamic parameters between the vasoreactive and non-vasoreactive subgroups. When stratifying by PVR, inhaled NO and O_2 reduced PVR by 50% (IQR 42%, 65%) in the vasoreactive subgroup and by 15% (IQR 6%, 20%) in the non-vasoreactive subgroup. When stratifying by mPAP, inhaled NO and O_2 decreased mPAP by 21% (IQR 15%, 25%) in the vasoreactive subgroup and by 4% (IQR -8%, +3%) in the non-vasoreactive subgroup. Kaplan-Meier survival analysis demonstrated a greater survival for those patients whose PVR decreased by at least 30% with inhaled NO and O_2 (Fig. 1). Similarly, PAH patients in whom inhaled NO and O_2 reduced mPAP by at least 12% exhibited greater survival (Fig. 2).

Adjusted Cox proportional hazard modeling using changes in PVR and PAP as dichotomous variables stratified about the median was also performed (Table 2). A 30% decrease in PVR with breathing inhaled NO and O_2 corresponded to a 53% reduction in age-adjusted mortality (HR 0.47, 95% CI 0.23-0.99, P=0.047) while a≥12% decrease in mPAP conferred a 55% reduction in mortality (HR 0.45, 95% CI 0.22-0.96, P=0.038). The hazard ratios remained significant after adjusting for age and other multivariate

Table 3: Characteristics of patients stratified by pulmonary vasoreactivity to inhaled NO and O_2

	Stratified by ΔPVR		Stratified by ΔmPAP	
	ΔPVR≥30% (*n*=41)	ΔPVR<30% (*n*=39)	ΔmPAP≥12% (*n*=40)	ΔmPAP<12% (*n*=40)
Age at RHC (years)	55±16	55±19	56±16	53±18
Gender - Female (%)	32 (78)	25 (64)	32 (80)	25 (63)
Diagnosis (%)				
IPAH or familial PAH	18 (44)	10 (26)	15 (38)	13 (33)
Collagen vascular disease	11 (27)	12 (31)	14 (35)	9 (23)
Portal hypertension	6 (15)	10 (26)	6 (15)	10 (25)
Clinical data				
WHO functional class I/II/ III-IV	3/13/25 (7/32/61)	1/9/29 (3/23/74)	4/12/24 (10/30/60)	0/10/30 (0/25/75)
Six-minute walk (m)†	370±170	300±150	340±150	380±200
Baseline hemodynamic parameters				
PVR (dynes-sec/cm^5)	840±480	870±690	760±430	950±700
mPAP (mmHg)	49±13	50±15	47±12	51±16
PCWP (mmHg)	10±4	10±4	10±4	10±4
Cardiac index (L/min/m^2)	2.6±0.9	2.5±1.0	2.6±0.9	2.5±1.0
Response to inhaled NO and O_2				
ΔPVR (% reduction)	50 (42, 65)	15 (6, 20)*	48 (29, 58)	19 (13, 30)*
ΔmPAP (% reduction)	21 (11, 25)	7 (0, 12)*	21 (15, 25)	4 (-3, 8)*

Vasoreactivity was defined as a change greater than or equal to the median value. Variables are presented as mean+SD, median (IQR), or n (%). Comparisons between vasoreactive and non-vasoreactive groups of patients were made using the Student t test or Mann-Whitney U statistic, as appropriate, for continuous variables and Fisher's exact test for categorical variables. The Kruskal-Wallis statistic was used to compare WHO functional classification. *P<0.05, comparing the above median and below median groups. †n=24 patients

predictors of survival: RA pressure, the presence of portopulmonary hypertension, and DLCO (Table 2). The age-adjusted Cox hazard ratio for the group of patients (n=30) that demonstrated vasoreactivity in both PVR (≥30% decrease) and mPAP (≥12% decrease) was 0.43 (95% CI 0.19-0.98, P=0.04), similar to the hazard ratio for each criterion alone.

The change in PVR while breathing NO and O_2 correlated with changes in mPAP (correlation coefficient r=0.59, P<0.001) and changes in CO (r=0.58, P<0.001). The median change in CO with inhaled NO and O_2 was 17% (IQR 6%, 39%). Changes in CO with vasodilator challenge did not predict survival and did not correlate with changes in mPAP. PCWP did not change significantly with vasodilator challenge (median change 0 mmHg, IQR 0,1 mmHg).

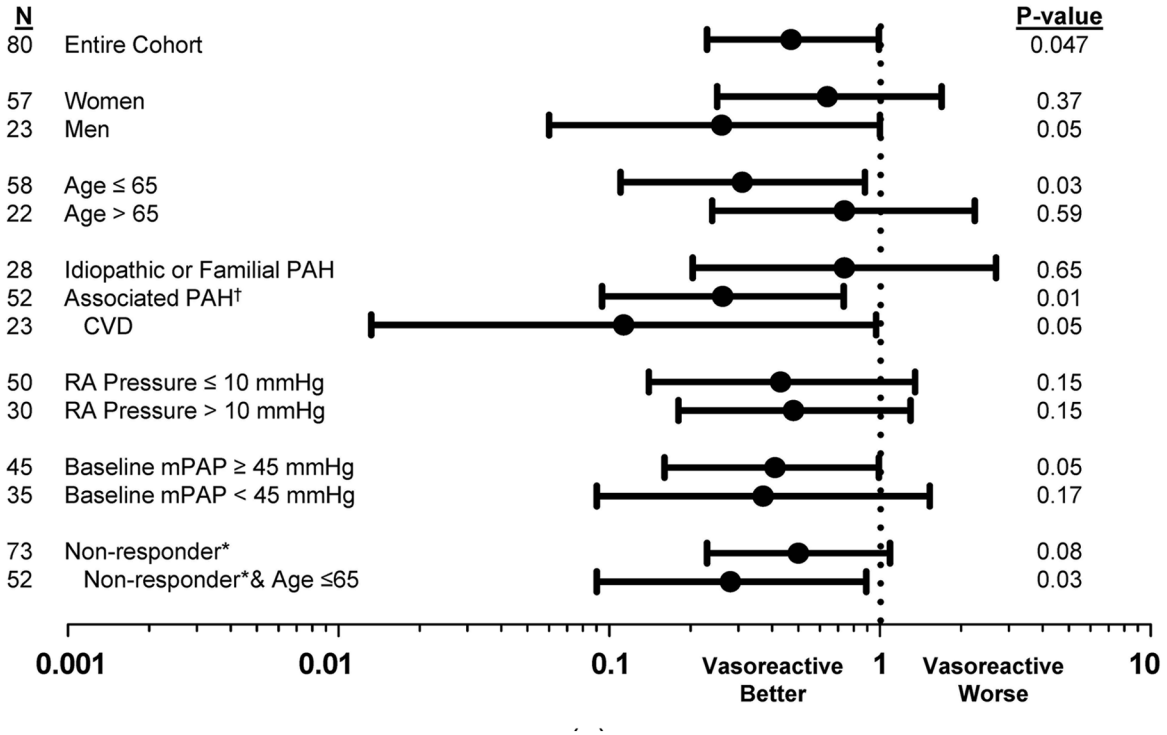
Prognostic value of vasoreactivity in patient subgroups

Having found that changes in PVR and mPAP while breathing NO and O_2 predict long-term survival in PAH, we then sought to determine whether this ability to predict survival was sustained across multiple subpopulations. Vasoreactivity defined as a ≥30% decrease in PVR (Fig. 3A) or ≥12% decrease in mPAP (Fig. 3B) with vasodilator challenge showed similar trends in multiple subgroups for improved survival. In the subgroup of APAH (n=52), the median reductions in PVR and mPAP were 26% (IQR 12%, 49%) and 11% (4%, 21%). Of patients with APAH, 23 patients (44%) exhibited a vasoreactive PVR response and 25 patients had a mPAP response (48%). APAH patients with vasoreactivity by either PVR or mPAP criteria had lower mortality compared to non-vasoreactive patients (HR 0.26, P=0.01, Fig. 3A and HR 0.29, P=0.02, Fig. 3B, respectively). For the subgroup with collagen vascular disease associated PAH (n=23), 11 exhibited a PVR vasodilator response (48%) and 14 had a mPAP response (61%). PVR responsiveness was associated with a Cox HR of 0.11 (95% CI 0.01-0.97, P=0.047) and mPAP responsiveness with a HR of 0.24 (95% CI 0.05-1.23, P=0.09).

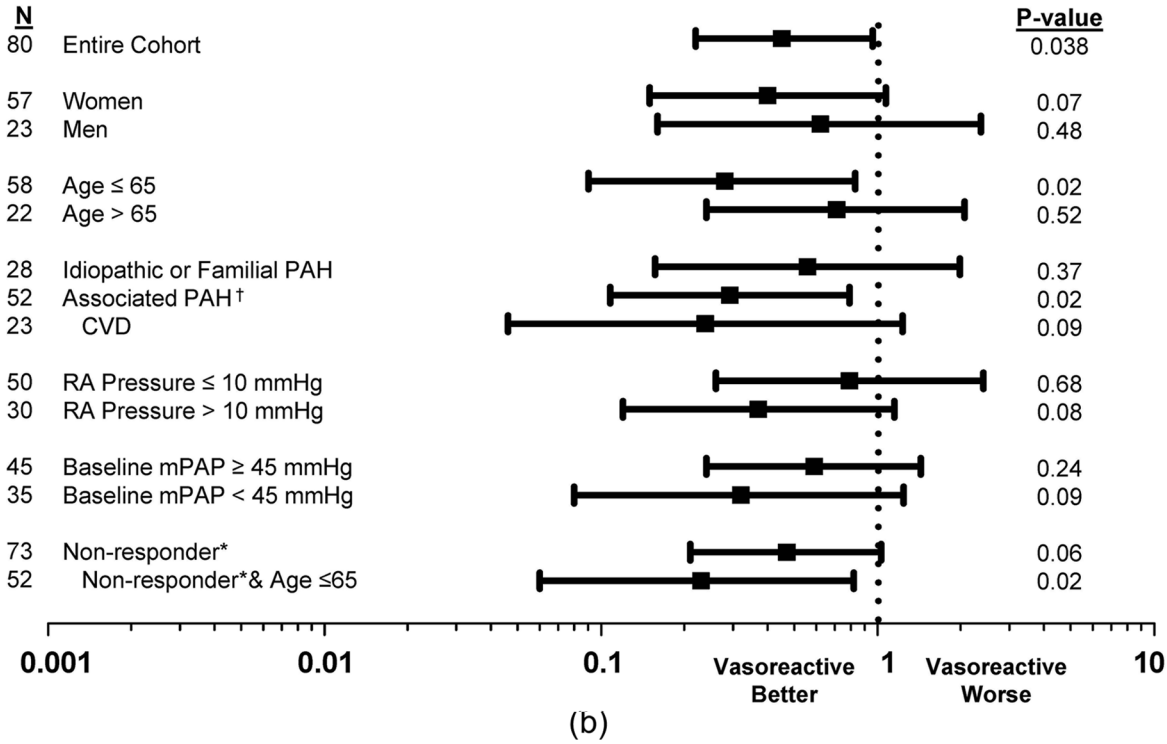
In the 52 patients (aged <65 years) deemed non-responsive by current guidelines,[4] a≥30% reduction in PVR with vasodilator challenge predicted improved survival (Cox HR 0.28, P=0.03, Fig. 3A). Similarly, a ≥12% reduction in mPAP during NO and O_2 inhalation predicted a 77% reduction in mortality (Cox HR 0.23, P=0.02, Fig. 3B).

PAH-specific treatment is described in Table 4. The use of epoprostenol, ETAs, and PDE5 inhibitors were similar in responders and non-responders. CCAs were used more frequently in the vasoreactive group, although this difference did not achieve statistical significance. There was no association between the use of any particular therapeutic agent and improved survival (Table 4).

Vasoreactivity in IPAH has been shown in prior studies to predict responsiveness to long-term CCA therapy,[8] but its importance in predicting survival in non-CCA



(a)



(b)

Figure 3: Changes in PVR and mPAP with inhaled NO and O_2 predict survival across multiple subpopulations of PAH. Forest plots of age-adjusted Cox proportional hazard ratios are depicted on a logarithmic scale, with ratios less than 1 indicating a favorable prognosis with vasoreactivity to inhaled NO and O_2. In **(A)**, vasoreactivity is defined as a≥30% decrease in PVR with vasodilator compared to baseline. In **(B)**, vasoreactivity is defined as a≥12% decrease in mPAP with vasodilator compared to baseline. * indicates vasodilator non-responsiveness by current guidelines.[3,4] † indicates PAH associated with collagen vascular disease (CVD), portal hypertension, congenital heart disease, HIV, anorexigen use, or Gaucher's disease.

treated patients has not been well established.[4] In the 66 patients who were never treated with CCA in our cohort, a≥30% reduction in PVR with vasodilator challenge predicted improved survival (Cox HR 0.42, P=0.04, Fig. 4A). Similarly, among the non-CCA patients, a≥12% reduction in mPAP during NO and O_2 inhalation predicted a 58% reduction in mortality (Cox HR 0.46, P=0.05, Fig. 4B).

Safety

No adverse events or reactions to inhaled NO and O_2 occurred during the acute vasodilator study.

DISCUSSION

This investigation demonstrates the prognostic utility of pulmonary vasoreactivity assessment with inhaled NO and O_2 in patients with PAH. Specifically, we observed that vasodilator-induced reductions in PVR and mPAP predicted better long-term survival. Stratifying patients by the median change in PVR or mPAP while breathing NO and O_2 identified high and lower risk PAH groups despite having similar baseline hemodynamic characteristics. Multivariate Cox regression analysis confirmed that the change in PVR or mPAP with inhaled NO and O_2 is an independent predictor of mortality, even after adjusting for other known predictors of outcome. Changes in cardiac output and PCWP with vasodilator challenge were not predictive of survival. Since PVR is a calculated variable derived from mPAP, PCWP, and cardiac output, it is the mPAP component that is critical in predicting survival in PAH. Although prior studies have utilized pulmonary vasodilator testing with inhaled NO to identify responders to CCA,[8,9,13-16] in this study we demonstrate that acute pulmonary vasoreactivity with NO and O_2 predicts long-term survival even among those patients not treated with CCA.

Univariate predictors of survival in our study population were age, RA pressure, the presence of portopulmonary hypertension, renal function, DLCO, and vasoreactivity. Unlike results from the NIH registry,[10,17] cardiac index was not a predictor of survival in our population. The mean cardiac index of 2.6±0.9 L/min/m^2 in our population was greater than observed in the NIH registry and may not be a predictor of survival at the time of diagnosis in a group of PAH patients at an earlier stage in their disease. Moreover, the hemodynamic characteristics of our cohort were similar to those of the recently published REVEAL trial[18] in which cardiac index was also not found to be a predictor of survival in multivariate analysis.

In 1985, Rich and colleagues first observed that an acute pulmonary vasodilator response in PAH with nifedipine and

Table 4: Subsequent treatment initiated in patients stratified by pulmonary vasoreactivity to inhaled NO and O_2

	Stratified by ΔPVR		Stratified by ΔmPAP		Cox hazard ratio for mortality (95% CI)
	ΔPVR≥30% (*n*=41)	ΔPVR<30% (*n*=39)	ΔmPAP≥12% (*n*=40)	ΔmPAP<12% (*n*=40)	
Epoprostenol	16 (39%)	19 (49%)	18 (45%)	17 (43%)	1.18 (0.58-2.39)
ET Antagonist	9 (22%)	12 (31%)	9 (23%)	12 (30%)	0.80 (0.34-1.86)
PDE 5 Inhibitor	19 (46%)	18 (46%)	22 (55%)	15 (38%)	0.92 (0.45-1.87)
CCA	10 (24%)	4 (10%)	10 (25%)	4 (10%)	0.45 (0.14-1.48)

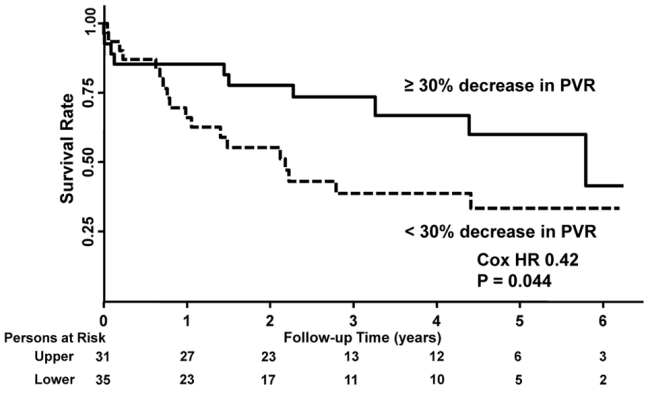


Figure 4a: Acute pulmonary vasoreactivity with inhaled NO and O_2 predicts survival in PAH patients not treated with calcium channel antagonists (CCA). Of the 66 PAH patients never treated with CCA, either a≥30% decrease in PVR (A) or a≥12% decrease in mPAP (B) with vasodilator at the time of diagnosis predicted improved Kaplan-Meier survival ($P \leq 0.05$ for both).

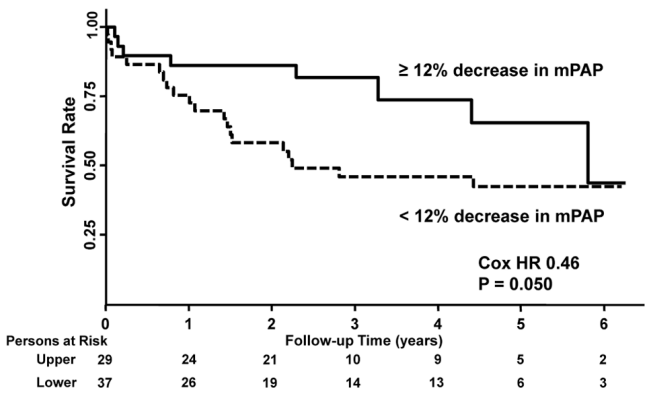


Figure 4b: Acute pulmonary vasoreactivity with inhaled NO and O_2 predicts survival in PAH patients not treated with calcium channel antagonists (CCA). Of the 66 PAH patients never treated with CCA, either a≥30% decrease in PVR (A) or a≥12% decrease in mPAP (B) with vasodilator at the time of diagnosis predicted improved Kaplan-Meier survival ($P \leq 0.05$ for both).

hydralazine is predictive of survival.[19] Current guidelines recommend inhaled NO as the preferred short-acting agent for pulmonary vasoreactivity testing.[4] Intravenous (IV) adenosine is an alternative agent for vasodilator testing and, in a univariate model, the acute change in PVR with adenosine administration has been shown to predict survival in PAH patients subsequently treated with epoprostenol.[11] However, adverse effects such as palpitations and dyspnea are commonly experienced with the administration of adenosine.[6,20] Short-term infusion of prostacyclin has also been used in acute pulmonary vasodilator testing and, in a univariate analysis, a >50% decrease in total pulmonary resistance index predicted improved two-year survival.[21] However, only 10% of patients were observed to have this degree of response and patients that did not respond received no treatment. When compared to the acute effects of IV epoprostenol, inhaled NO was found to be a better predictor of long-term clinical outcome in PAH patients treated with oral vasodilators.[14] Although inhaled NO is the preferred agent in vasodilator testing to guide the use of CCA,[4] its role in predicting outcomes in the PAH population is not established. This study now demonstrates that the acute pulmonary vasodilator response to inhaled NO and O_2 adds to the prognostic value of other variables such as age and RA pressure in predicting survival in PAH patients.

The definitions used in this investigation for a positive vasodilator response differ from those of current guidelines. The guideline-based criteria have been validated to identify the minority of PAH patients (10-15%)[6] who respond to CCA therapy. The patients in our investigation meeting criteria for vasoreactivity by the current guidelines demonstrated a trend towards improved survival (HR 0.66, 95% CI 0.16-2.80). The thresholds for vasoreactivity utilized in this study–determined by population median values–effectively stratify the PAH population into high and lower risk mortality groups. Three-year survival for vasoreactive patients was 80% compared to only 48% in non-vasoreactive patients (Figs. 1 and 2). Survival in non-vasoreactive patients of our study (median survival 2.8 years) was the same as that reported in patients of the NIH registry,[10] despite the greater use of PAH-specific therapies in the present era. However, non-vasoreactive patients in the present study were older than those followed in the original NIH registry (55±19 vs. 36±15 years),[10,22] perhaps explaining the similarities in their survival despite the differences in their treatments.

Current guidelines recommend pulmonary vasodilator testing only in patients with IPAH.[4] However, pulmonary vasoreactivity has been described and, in some cases, utilized to guide therapy in APAH.[23-25] In this investigation, we found that vasoreactivity with inhaled NO and O_2 was predictive of long-term survival in APAH patients (Fig. 3, A and B). Further study is warranted to determine if the broader applicability of vasodilator testing in PAH patients is indicated to guide chronic management. The utility of vasodilator testing has been well established to identify those PAH patients more likely to have a sustained benefit from CCA treatment.[4] This study suggests that there is prognostic value of vasodilator testing even in patients who are not candidates for CCA treatment.

Limitations

This study was performed in a retrospective manner and included a sample size of 80 patients; hence, the results, in particular the subgroup analyses, must be considered hypothesis generating and warrant further investigation prospectively. Patients were not randomized to PAH-specific therapies and, therefore, this may confound comparisons of survival between vasoreactive and non-vasoreactive groups. This study included patients with WHO Group I PAH, but the broader applicability of acute vasodilator testing in other forms of pulmonary hypertension has not been elucidated. Patient survival was not assessed prospectively in this study, but no patients were lost to follow-up. Moreover, we administered 80 ppm NO with 90% O_2 for acute pulmonary vasodilator testing, as is our standard practice. Further study is needed to determine if our findings are applicable to the response of PAH patients breathing different concentrations of NO and oxygen. Methemoglobin levels were not assayed in this study, but have been assayed in prior studies utilizing the same protocol and found to be at safe levels (<1.5%).[26]

CONCLUSIONS

This investigation demonstrates that pulmonary vasodilator testing with inhaled NO and O_2 can be used to identify subpopulations of PAH patients with high and lower risk of mortality. Further investigation is needed to determine if these high-risk PAH patients would benefit from a more aggressive therapeutic strategy.

ACKNOWLEDGMENTS

This work was performed at the Massachusetts General Hospital in Boston, Massachusetts.

REFERENCES

1. Farber HW, Loscalzo J. Pulmonary arterial hypertension. N Engl J Med 2004;351:1655-65.
2. Simonneau G, Robbins IM, Beghetti M, Channick RN, Delcroix M, Denton CP, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2009;54:S43-54.
3. Barst RJ, Gibbs JS, Ghofrani HA, Hoeper MM, McLaughlin VV, Rubin LJ,

et al. Updated evidence-based treatment algorithm in pulmonary arterial hypertension. J Am Coll Cardiol 2009;54:S78-84.
4. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. J Am Coll Cardiol 2009;53:1573-619.
5. Badesch DB, Abman SH, Ahearn GS, Barst RJ, McCrory DC, Simonneau G, et al. Medical therapy for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest 2004;126:35S-62S.
6. Tonelli AR, Alnuaimat H, Mubarak K. Pulmonary vasodilator testing and use of calcium channel blockers in pulmonary arterial hypertension. Respir Med 2010;104:481-96.
7. Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. N Engl J Med 1992;327:76-81.
8. Sitbon O, Humbert M, Jais X, Ioos V, Hamid AM, Provencher S, et al. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. Circulation 2005;111:3105-11.
9. Sitbon O, Humbert M, Jagot JL, Taravella O, Fartoukh M, Parent F, et al. Inhaled nitric oxide as a screening agent for safely identifying responders to oral calcium-channel blockers in primary pulmonary hypertension. Eur Respir J 1998;12:265-70.
10. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Ann Internal Med 1991;115:343-9.
11. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: The impact of epoprostenol therapy. Circulation 2002;106:1477-82.
12. Galie N, Torbicki A, Barst R, Dartevelle P, Haworth S, Higenbottam T, et al. Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. Eur Heart J 2004;25:2243-78.
13. McLaughlin VV, Genthner DE, Panella MM, Rich S. Reduction in pulmonary vascular resistance with long-term epoprostenol (prostacyclin) therapy in primary pulmonary hypertension. N Engl J Med 1998;338:273-7.
14. Morales-Blanhir J, Santos S, de Jover L, Sala E, Paré C, Roca J, et al. Clinical value of vasodilator test with inhaled nitric oxide for predicting long-term response to oral vasodilators in pulmonary hypertension. Respir Med 2004;98:225-34.
15. Ricciardi MJ, Knight BP, Martinez FJ, Rubenfire M. Inhaled nitric oxide in primary pulmonary hypertension: A safe and effective agent for predicting response to nifedipine. J Am Coll Cardiol 1998;32:1068-73.
16. Sitbon O, Brenot F, Denjean A, Bergeron A, Parent F, Azarian R, et al. Inhaled nitric oxide as a screening vasodilator agent in primary pulmonary hypertension. A dose-response study and comparison with prostacyclin. Am J Respir Crit Care Med 1995;151:384-9.
17. Thenappan T, Shah SJ, Rich S, Tian L, Archer SL, Gomberg-Maitland M. Survival in pulmonary arterial hypertension: A reappraisal of the NIH risk stratification equation. Eur Respir J;35:1079-87.
18. Benza RL, Miller DP, Gomberg-Maitland M, Frantz RP, Foreman AJ, Coffey CS, et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). Circulation 2010;122:164-72.
19. Rich S, Brundage BH, Levy PS. The effect of vasodilator therapy on the clinical outcome of patients with primary pulmonary hypertension. Circulation 1985;71:1191-6.
20. Jing ZC, Jiang X, Han ZY, Xu XQ, Wang Y, Wu Y, et al. Iloprost for pulmonary vasodilator testing in idiopathic pulmonary arterial hypertension. Eur Respir J 2009;33:1354-60.
21. Raffy O, Azarian R, Brenot F, Parent F, Sitbon O, Petitpretz P, et al. Clinical significance of the pulmonary vasodilator response during short-term infusion of prostacyclin in primary pulmonary hypertension. Circulation 1996;93:484-8.
22. Rich S, Dantzker DR, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, et al. Primary pulmonary hypertension. A national prospective study. Ann Internal Med 1987;107:216-23.
23. Haworth SG, Hislop AA. Treatment and survival in children with pulmonary arterial hypertension: the UK Pulmonary Hypertension Service for Children 2001-2006. Heart 2009;95:312-7.
24. Krasuski RA, Warner JJ, Wang A, Harrison JK, Tapson VF, Bashore TM. Inhaled nitric oxide selectively dilates pulmonary vasculature in adult patients with pulmonary hypertension, irrespective of etiology. J Am Coll Cardiol 2000;36:2204-11.
25. Strange C, Bolster M, Mazur J, Taylor M, Gossage JR, Silver R. Hemodynamic effects of epoprostenol in patients with systemic sclerosis and pulmonary hypertension. Chest 2000;118:1077-82.
26. Semigran MJ, Cockrill BA, Kacmarek R, Thompson BT, Zapol WM, Dec GW, et al. Hemodynamic effects of inhaled nitric oxide in heart failure. J Am Coll Cardiol 1994;24:982-8.

Source of Support: This work was supported by National Institutes of Health grants [Grants T32HL007208 (RM), K23HL091106 (GDL), and K24HL004021 (MJS)] from the National Heart, Lung, and Blood Institute. Conflicts of Interest: Dr. Bloch's laboratory is supported in part by a sponsored research agreement between Massachusetts General Hospital and Ikaria. Dr. Bloch has obtained patents relating to the use of inhaled nitric oxide. These patents are assigned to Massachusetts General Hospital, which has licensed them to Ikaria (Clinton, NJ) and Linde Gas Therapeutics (Lidingo, Sweden). Dr. Waxman serves on the Scientific Advisory Boards of United Therapeutics Corporation and Pfizer Inc., and receives research funding from Gilead Sciences Inc., Medtronic Inc., Bayer Pharmaceuticals, and Actelion Pharmaceuticals Ltd. Drs. Malhotra, Hess, Lewis, and Semigran have no potential, **Conflict of Interest:** None declared.