## Clinical Trials

# Response to Inhaled Nitric Oxide Predicts Survival in Patients With Pulmonary Hypertension

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**ABSTRACT**

**Objective:** To examine the ability of vasodilator response to predict survival in a diverse cohort of patients with pulmonary hypertension (PH).

**Patients & Methods:** A total of 214 consecutive treatment-naive patients referred for invasive PH evaluation were enrolled between November 1998 and December 2008. Vasoreactivity was assessed during inhalation of 40 parts per million nitric oxide (iNO) and vasodilator responders were defined as those participants who achieved a mean pulmonary artery pressure (PAP) of $\leq$ 40 mm Hg and a drop in mean PAP $\geq$ the median for the cohort (13%). Kaplan-Meier analysis and Cox proportional hazards modeling were used to identify predictors of survival.

**Results:** There were 51 deaths (25.9%) over a mean follow-up period of 2.3 years. Kaplan-Meier analysis demonstrated that vasodilator responders had significantly improved survival ($P < .01$). Vasodilator responders had improved survival regardless of whether or not they had idiopathic or nonidiopathic PH ($P = .02$, $P < .01$) or whether or not they had Dana Point class 1 or non-Dana Point class 1 PH ($P < .01$, $P = .01$). In multivariate modeling, advanced age, elevated right atrial pressure, elevated serum creatinine, and worsened functional class significantly predicted shorter survival ($P = .01$, $P = .01$, $P = .01$, $P < .01$), whereas vasodilator response predicted improved survival ($P = .01$).

**Conclusions:** Vasodilator responsiveness to iNO is an important method of risk stratifying PH patients, with results that apply regardless of clinical etiology. (*J Cardiac Fail 2011;17:265–271*)

**Key Words:** Vasodilator challenge, pulmonary hypertension, pulmonary arterial hypertension, mortality.

Pulmonary hypertension (PH) is a devastating disease characterized by endothelial dysfunction of the small pulmonary arteries.[1,2] Three general abnormalities of these vessels have been noted: inappropriate smooth muscle proliferation and abnormal remodeling, dysfunctional hemostasis favoring thrombosis, and abnormal regulation of vascular tone. These changes lead to progressive increases in the pulmonary artery (PA) pressure and pulmonary vascular resistance (PVR) and eventually result in right ventricular failure and death.[3]

The natural history of the disease was originally characterized by a National Institutes of Health registry which showed survival rates of 68%, 48%, and 34% at 1, 3, and 5 years, respectively.[4] Medical therapy for PH has greatly advanced over the past decade, particularly with the development of prostaglandins,[5–7] endothelin antagonists,[8–13] and selective phosphodiesterase inhibitors.[14–16] Unfortunately, these medications remain costly and are limited by drug-specific toxicities.[10,17] Guidelines and position papers have established pulmonary vasodilator testing as an appropriate first step in selecting therapy.[18,19] Rich and colleagues published the seminal study establishing the role for assessing pulmonary vasoreactivity in 1992.[20] They

administered calcium channel blockers to 64 patients with idiopathic pulmonary hypertension and found a 26% response rate according to a definition of 20% drop in PA pressure and PVR. Responders were then treated indefinitely with high doses of calcium channel blockers. Survival in acute responders was 95% at 5 years, whereas only ~36% of nonresponders and historical controls had survived at 5 years. Despite the importance of these findings, several issues remained unaddressed after this landmark study. First and foremost, it was unclear whether the improved survival was the result of preserved vasodilator response or secondary to the long-term therapy with calcium channel blockers. Second, patients outside the spectrum of idiopathic PH were not examined, and thus the applicability of testing to the larger population of patients encompassed in the modern classification of PH[21,22] remained unclear. This question is particularly important considering recent data suggesting that vasodilator testing may have utility in patients with nonidiopathic disease such as PH from congenital heart disease[23] and chronic thromboembolic disease.[24] Third, as Sitbon et al. demonstrated, many of those patients identified by vasodilator challenge to be early responders to calcium channel blockers did not sustain benefits over the long term.[25] This finding, as well as recent therapeutic advances, makes it unclear whether the use of more modern medical therapies would offset the prognostic ability of vasodilator testing. Finally, published studies have used several different definitions of a "positive vasodilator response"; this has resulted in much confusion.[26–35] Acceptance of the most recent standard, a drop in mean PA pressure of ≥10 mm Hg coupled with mean PA pressure of ≤40 mm Hg, also remains far from universal.[36]

In light of these complexities, we designed a prospective cohort study to examine the utility of vasodilator testing with inhaled nitric oxide (iNO) to predict survival in PH. Because of its pulmonary selectivity and its short half-life, iNO has become the favored agent for testing; our group and others have previously established the safety of its use for this indication.[37,38]

## Methods

This study was approved by the Duke University Medical Center and the Cleveland Clinic institutional review boards. The study and manuscript are also in compliance with the provisions of the Health Insurance Portability and Accountability Act of 1996.

### Study Sample

A diverse cohort of consecutive patients with newly diagnosed PH of various etiologies was enrolled between November 1998 and December 2008. Patients with known Dana Point class 2 disease (PH with a primary venous component) were excluded from analysis as prespecified. Patients underwent cardiac catheterization for vasodilator testing as part of their diagnostic workup before initiation of therapy or further clinical intervention.

### Hemodynamic Measurement

All studies were conducted in the fasting state, with minimal sedation and were performed or supervised by the same primary operator (R.A.K.). If a left heart catheterization was performed, all contrast injections were performed after hemodynamic assessments were completed. Right heart catheterization was performed using a single end-hole, balloon flotation catheter (Bard Pulmonary Wedge Catheter, Medtronic, Minneapolis, MN or Balloon Wedge Pressure Catheter, Arrow International, Reading, PA). Baseline hemodynamic measurements included mean right atrial pressure; right ventricular systolic and diastolic pressures; PA systolic, diastolic, and mean pressures; mean pulmonary capillary wedge (pulmonary artery occlusive) pressure; and femoral artery systolic, diastolic, and mean pressures. Repeat measurements during drug administration 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 index using the Fick method at baseline and during drug administration. Systemic and pulmonary vascular resistances were calculated using standard hemodynamic equations and are presented in absolute (Wood) units.

### Nitric Oxide Delivery Protocol

The techniques for delivery of nitric oxide have been well described previously.[39] iNO gas (INO Therapeutics; Madison, WI) of medical-grade quality, conforming to US Food and Drug Administration standards, was used. A specialized delivery device (INOvent Delivery System, Ohmeda Inc, Madison, WI) delivered NO from source tanks to achieve proper dosing. All patients received iNO at 40 parts per million. At least 5 minutes were allowed before hemodynamic assessment was undertaken and pulmonary and femoral artery blood samples were repeatedly drawn for Fick cardiac output determination.

### Clinical Assessment and Follow-up

All patients underwent full clinical evaluation at the time of initial referral for cardiac catheterization. Baseline studies included chest radiography, chest computed tomography if chest radiography was abnormal, ventilation-perfusion scanning, full pulmonary function testing, and electrocardiography. Subsequent medical therapy was administered at the discretion of the referring physicians. Patients were followed at regularly scheduled intervals and were also contacted by telephone at the completion of the study to verify vital status, initially assessed through examination of the Social Security Death Index.

### Statistical Analysis

Data are presented as mean ± standard deviation for continuous variables and as a percentage for discrete variables. Comparison of dichotomous variables was performed using the Pearson chi-squared test or Fisher's exact test where appropriate. Comparisons of continuous variables between groups were performed using 2-sided $t$-tests. The Kaplan-Meier method was used to compute unadjusted survival functions and the difference was tested using a log-rank test. Multivariate analysis was performed using Cox proportional hazards, and inclusion in the model was determined by significance on univariate analysis as well as the external clinical judgment of the investigators. The proportional hazards assumption was tested and upheld graphically. For all tests

**Table 1.** Baseline Characteristics of Pulmonary Hypertensives Stratified by Vital Status at Completion of Follow-up Period

| Demographics | All Patients (n = 197) | Survivors (n = 146) | Deaths (n = 51) | P Value |
|---|---|---|---|---|
| Age (y) | 56.4 (14.6) | 54.3 (14.3) | 62.2 (14.1) | **<.01** |
| Female (%) | 72 | 72 | 73 | 1.00 |
| Race (%) | | | | .58 |
|   Caucasian | 80 | 81 | 77 | |
|   African American | 17 | 16 | 22 | |
|   Other | 3 | 3 | 2 | |
| Modified Dana Point Classification (%) | | | | .92 |
|   Class 1 | 68 | 67 | 69 | |
|   Class 3 | 20 | 20 | 22 | |
|   Class 4 | 4 | 4 | 4 | |
|   Class 5 | 8 | 9 | 6 | |
| Idiopathic pulmonary hypertension (%) | 43 | 43 | 41 | .87 |
| WHO class ≥ III (%) | 68.4 | 62.0 | 87.5 | **<.01** |
| Systemic hypertension (%) | 33 | 34 | 29 | .61 |
| Diabetes (%) | 17 | 16 | 20 | .67 |
| Atrial fibrillation (%) | 14 | 12 | 22 | .10 |
| Serum sodium (mg/dL) | 139.0 (3.3) | 139.3 (3.0) | 138.3 (4.1) | .11 |
| Serum creatinine (mg/dL) | 1.0 (0.4) | 1.0 (0.4) | 1.1 (0.4) | **.01** |
| Arterial oxygen saturation (%) | 89.0 (14.8) | 89.9 (14.3) | 86.9 (15.8) | .32 |
| At least 1 pulmonary hypertension drug (%)* | 60 | 60 | 61 | 1.00 |
| Combination pulmonary hypertension drug (%)* | 17 | 19 | 12 | .28 |

Continuous variables are presented as mean values (standard deviations).
Bold values indicate statistical significance.
*Percent of patients started on pulmonary hypertension−specific therapy during follow-up.

a P value <.05 was considered statistically significant. Data were analyzed and compiled using JMP 8.0 software (SAS Institute, Inc, Cary, NC).

## Results

### Patient Demographics and Baseline Hemodynamics

Catheterization and nitric oxide challenge were performed on 214 patients. Fifteen patients were excluded for predominately pulmonary venous hypertension (Dana Point class 2). Two patients were excluded because operators were unable to enter the pulmonary artery because of severe anatomic distortion: one patient with pulmonary atresia and 1 with congenitally corrected transposition who experienced ventricular tachycardia during catheter manipulation. Final analysis was conducted using the remaining 197 patients. There were 51 deaths (25.9%) over a mean follow-up period of 2.3 years. The demographics of the entire population, stratified by their vital status at the completion of the follow-up period, are listed in Table 1.

The cohort of decedents was older (62.2 ± 14.4 years vs. 54.3 ± 14.3 years, $P < .01$) and had more progressive functional impairment compared to survivors (World Health Organization class ≥ III, 87.5 vs. 62.0%, $P < .01$). Decedents also had a higher serum creatinine than survivors (1.1 ± 0.4 vs. 1.0 ± 0.4 mg/dL, $P = .01$). The distribution of pulmonary hypertension classifications did not appear different between decedents and survivors (Dana Point class 1/3/4/5, 69/22/4/6 vs. 67/20/4/9%, $P = .92$), nor did the distribution of patients with idiopathic PH (43.2 vs. 41.2%, $P = .87$).

Baseline hemodynamic values, stratified by vital status, are listed in Table 2. Decedents had higher RA pressure (12.5 ± 6.6 vs. 9.3 ± 5.5 mm Hg, $P < .01$) and mean PA pressure (49.6 ± 16.9 vs. 44.4 ± 15.5 mm Hg, $P = .05$) than survivors, though cardiac index was similar (2.3 ± 0.9 and 2.5 ± 0.9 L·min·m², $P = .14$).

### Response to Nitric Oxide Challenge

The mean reduction in PA pressure during iNO compared with baseline was 14.1 ± 12.6% in the entire population and the median reduction was 13.3% (interquartile

**Table 2.** Baseline Hemodynamic Values stratified by Survivors Versus Deaths

| Demographics | All Patients (n = 197) | Survivors (n = 146) | Deaths (n = 51) | P Value |
|---|---|---|---|---|
| RA pressure, mm Hg | 10.2 (5.9) | 9.3 (5.5) | 12.5 (6.6) | **<.01** |
| PA pressure, mm Hg | 45.8 (15.7) | 44.4 (15.5) | 49.6 (15.9) | .05 |
| Cardiac index, L/m²/min | 2.5 (0.9) | 2.5 (0.9) | 2.3 (0.9) | .14 |
| PVR, Wood units | 9.1 (7.2) | 8.4 (7) | 10.6 (7.5) | .11 |
| SVR, Wood units | 22.2 (9.1) | 22.3 (9.2) | 22.0 (8.9) | .87 |
| Vasodilator responder (%) | 39.1 | 46.6 | 17.7 | **<.01** |

RA, right atrium; PA, pulmonary arterial; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.
Continuous variables are presented as mean values (standard deviations).
Bold values indicate statistical significance.
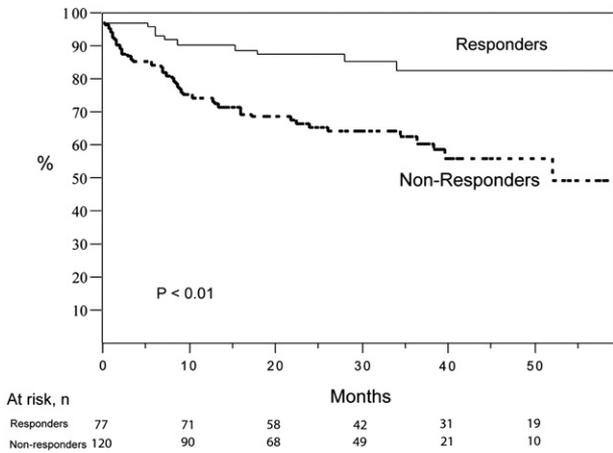
**Fig. 1.** Kaplan-Meier survival analysis of all patients dichotomized by vasodilator response.

range: 0.05% to 22.7%). When stratified according to vital status, a trend toward greater reduction in PA pressure ($15.6 \pm 12.6\%$ vs. $9.7 \pm 11.5\%$, $P < .01$) was seen in patients who survived compared to those who died. PA pressure reduction did not appear to vary according to PH classification.

We chose to define vasodilator responders as those participants who achieved both a PA pressure $\leq 40$ mm Hg and at least the median reduction in PA pressure of the cohort (13.3%). Kaplan-Meier survival analysis of the entire cohort demonstrates improved survival for vasodilator responders versus non-responders ($P < .01$, Fig. 1). Furthermore, being a vasodilator responder predicted improved survival regardless of whether the patient had idiopathic or nonidiopathic PH ($P = .02$, $P < .01$; Fig. 2), and whether or not they had Dana Point Class 1 or non-Dana Point Class 1 PH ($P < .01$, $P = .01$; Fig. 3).

Clinical characteristics are stratified by vasoreactivity in Table 3. Vasodilator responders were less likely to receive PH-specific therapy (39% vs. 73%, $P < .01$) or a combination of PH-specific therapies (9.1% vs. 22.5%, $P = .02$.

Vasodilator responders also had significantly lower RA pressures ($7.8 \pm 4.2$ mm Hg vs. $11.7 \pm 6.4$ mm Hg, $P < .01$), lower PA pressures ($39 \pm 10.6$ vs. $50.1 \pm 16.9$, $P < .01$), lower PVR ($6.6 \pm 5$ Woods Units vs. $10.7 \pm 8$ Woods Units, $P < .01$), and a higher cardiac index ($2.8 \pm 0.9$ vs. $2.3 \pm 0.9$, $P < .01$).

The variables included in the proportional hazards model were: age, baseline RA pressure, serum creatinine, function class, diagnostic class, and whether or not the participant was a vasodilator responder (Table 4). In the final model advanced age, elevated right atrial pressure, elevated serum creatinine, and worsened functional class significantly predicted shorter survival ($P = .01$, $P = .01$, $P = .01$, $P < .01$), whereas vasodilator response predicted improved survival with a hazard ratio of 0.35 ($P = .01$, Table 3). The addition of whether or not a patient received pulmonary arterial hypertension-specific therapy to the model did not appear to significantly alter the results, and had a nonsignificant parameter effect (HR 0.7, 95% CI 0.37-1.33, $P = .26$).

### Treatment During Follow-Up

The most commonly used pharmacologic agents in descending order of frequency included warfarin (49.3%), continuous flow oxygen (34.0%), angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (29.8%), epoprostenol (20.3%), sildenafil (27.4%), spironolactone (21.3%), bosentan (19.3%), statins (19.8%), digoxin (14.2%), treprostinil (8.1%), and iloprost (3.0%). The prevalence of PH-specific pharmacologic therapy during follow-up was not significantly different between survivors and decedents (Table 1). Four patients proceeded to lung transplantation during follow-up.

### Discussion

This study demonstrates that even in the context of more modern medical therapy, a drop in PA pressure with nitric oxide predicts an improved clinical outcome in patients
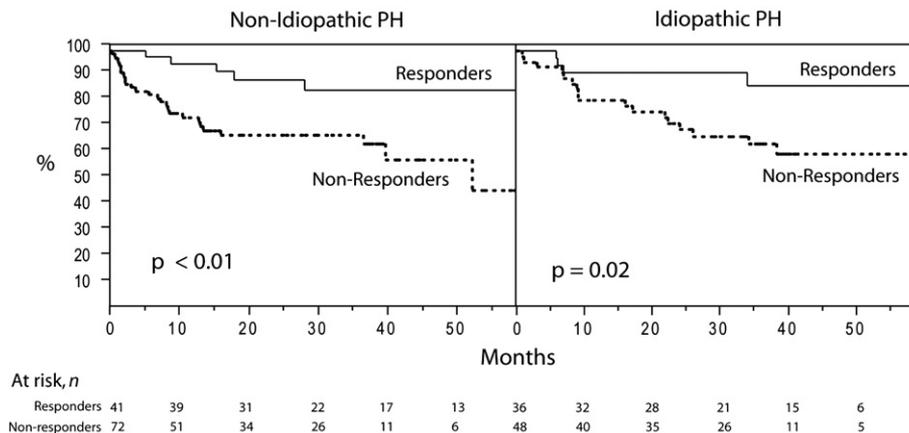


**Fig. 2.** Kaplan-Meier survival analysis of patients with both nonidiopathic and idiopathic pulmonary hypertension dichotomized by vasodilator response.
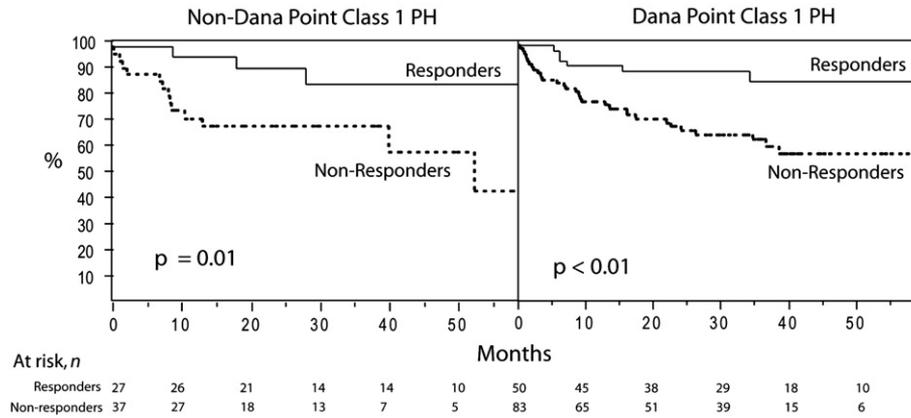
**Fig. 3.** Kaplan-Meier survival analysis of patients with both non-Dana Point class 1 and Dana Point class 1 pulmonary hypertension dichotomized by vasodilator response.

with treatment-naive PH. This difference was not only present in patients with idiopathic PH, but was similarly predictive of clinical outcome in nonidiopathic PH. Furthermore, vasodilator response predicted improved survival in both Dana Point class 1 PH and non-Dana Point class 1 PH. These findings suggest that vasoreactivity is a meaningful parameter for risk stratification, not only in those patients with idiopathic PH, but for the larger group of patients with PH of any classification (excluding those with pulmonary venous hypertension, Dana Point class II).

The cut point we used to define vasodilator responders was at least a 13.3% drop in PAP (the median reduction) to a value ≤40 mm Hg. Patients that met these criteria for vasodilator response experienced one-third the mortality of non-responders over a mean of 2.3 years. Not only did this trend hold true regardless of the etiology of PH, but

vasodilator response was found on multivariate analysis to be a strong predictor of improved survival even after adjustment for differences in age, creatinine, hemodynamics, function class, and diagnostic class. Therefore we maintain that vasodilator responsiveness has clinical utility for stratifying risk of mortality in a wider range of PH etiologies than those previously considered. It is also of note that this cut point identifies a larger group of vasodilator responders than other standards (such as a drop of 10 mm Hg to <40 mm Hg), and therefore may be selecting a broader group of patients that could potentially benefit from modern therapies. The application of this cut point, of course, must be validated in another cohort.

Because referring physicians were not blinded to testing results, confounding through therapy selection remains possible. Of note, no significant differences were seen between

**Table 3.** Clinical Characteristics Stratified by Vasoreactivity

| Demographics | All Patients (n = 197) | Responders (n = 77) | Nonresponders (n = 120) | P Value |
|---|---|---|---|---|
| Age (y) | 56.4 (14.6) | 55.6 (14.7) | 56.8 (14.8) | .56 |
| Female (%) | 72 | 66 | 75 | .14 |
| Race (%) | | | | .9 |
| Caucasian | 80 | 81 | 78 | |
| African American | 17 | 16 | 18 | |
| Other | 3 | 3 | 4 | |
| Modified Dana Point Classification (%) | | | | .42 |
| Class 1 | 68 | 65 | 69 | |
| Class 3 | 20 | 21 | 20 | |
| Class 4 | 4 | 3 | 5 | |
| Class 5 | 8 | 11 | 6 | |
| Idiopathic PH (%) | 43 | 43 | 40 | .39 |
| WHO Class ≥ III (%) | 68.4 | 61 | 74 | .08 |
| RA Pressure, mm Hg | 10.2 (5.9) | 7.8 (4.2) | 11.7 (6.4) | <.01 |
| PA pressure, mm Hg | 45.8 (15.7) | 39 (10.6) | 50.1 (16.9) | <.01 |
| Cardiac index, L/m$^2$/min | 2.5 (0.9) | 2.8 (0.9) | 2.3 (0.9) | <.01 |
| PVR, Wood units | 9.1 (7.2) | 6.6 (5) | 10.7 (8) | <.01 |
| SVR, Wood units | 22.2 (9.1) | 20.9 (9.3) | 23.1 (8.9) | .14 |
| At least 1 PH drug (%)* | 60 | 39 | 73 | <.01 |
| Combination PH drug (%)* | 17 | 9.1 | 22.5 | .02 |

RA, right atrium; PA, pulmonary arterial; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; WHO, World Health Organization.

Continuous variables are presented as mean values (standard deviations)

*Percent of patients started on PH-specific therapy during follow-up.

**Table 4.** Proportional Hazards Regression Model

| Variable | Hazard Ratio | 95% CI | *P* Value |
|---|---|---|---|
| Age | 1.03 | 1.01−1.05 | **.01** |
| Baseline RA pressure (mm Hg) | 1.07 | 1.02−1.12 | **.01** |
| Serum creatinine (mg/dL) | 2.20 | 1.18−3.68 | **0.01** |
| WHO class | 3.24 | 1.46−8.63 | **<.01** |
| Dana Point Class I | 1.21 | 0.66−2.36 | **.53** |
| Vasodilator vesponder | 0.35 | 0.14−0.74 | **.01** |

RA, right atrium; PA, pulmonary arterial; WHO, World Health Organization. Bold values indicate statistical significance.

the therapies utilized in responders and nonresponders, though this not surprising given that the variety of different therapies used limits the power to detect any meaningful survival differences within and between drug classes. Additionally, only 36% of patients with Dana Point Class 1 disease received pulmonary arterial hypertension specific therapy. Though the untreated patients may account for deaths that are independent of vasodilator response, treatment was not a predictor of death in multivariate modeling and the percentage of untreated patients was nearly identical between survivors and decedents (40% and 39%, respectively; *P* = 1.0). Another possible limitation of this study is that selection bias influenced referral for vasodilator testing. This could have affected the degree of vasodilator responsiveness and limited the applicability of the results. Of note it is standard practice at our institutions for all patients undergoing right heart catheterization for suspected or known PH to undergo vasodilator testing at the time of initial cardiac catheterization. A concerted effort was made to recruit all such patients referred for testing during the enrollment period, and the result is a diverse population of patients with PH. Additionally, enrollment in this study also occurred over a 10-year period, during which standard therapy changed significantly.

Because most previous studies have focused on patients with idiopathic PH or PH resulting from collagen vascular disease, this study provides novel information about a larger and previously understudied population of patients, those with PH of other etiologies. It is hoped that these findings will stimulate further research on the role of vasodilator challenge and its utility in identifying those patients who will benefit from therapy. Furthermore, a growing body of literature suggests use of endothelin antagonists,[40−42] phosphodiesterase inhibitors,[43−45] prostaglandins,[46] and combinations thereof[47,48] may improve PH outcomes in these patients. These findings are further supported by a recent meta-analysis showing that these targeted therapies do in fact improve survival.[49] Our results suggest that vasodilator testing continues to have prognostic utility, even with the advent of modern therapy. The mortality in this study (26% overall and 35% in nonresponders) again underscores the serious nature of a diagnosis of pulmonary hypertension. Clearly, there remains a continued need for investigation into the etiology of and therapeutic approach towards PH. In the meantime, vasodilator testing appears to be a very formidable manner of risk-stratifying patients with PH of various etiologies and identifying those patients at greatest need for aggressive medical therapy or consideration for lung or combined heart-lung transplantation.

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