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RESEARCH ARTICLE

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# Acute vasoreactivity testing during right heart catheterization in chronic thromboembolic pulmonary hypertension: Results from the pulmonary vascular disease phenomics study

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## Abstract

Chronic thromboembolic pulmonary hypertension (CTEPH) is believed to involve both vascular obstruction and vasoconstriction; hence, pulmonary vasodilators such as riociguat may be beneficial. Acute vasoreactivity testing (AVT) is seldom performed routinely in CTEPH patients, so there is limited understanding of the frequency and significance of an acute vasodilator response. Systematic vasodilator testing with oxygen ($O_2$) and oxygen plus inhaled nitric oxide ($O_2$ + iNO) was performed as part of the Pulmonary Vascular Disease Omics (PVDOMICS) NHLBI project, providing an opportunity to examine AVT responses in CTEPH. Patients with CTEPH enrolled in PVDOMICS ($n = 49$, 40 with prevalent CTEPH [82%]) underwent right heart catheterization including AVT with $O_2$ and $O_2$ + iNO. Hemodynamics were obtained at baseline and with each challenge. Fourteen of 49 patients (29%) had >20% drop in pulmonary vascular resistance (PVR) with $O_2$. With $O_2$ + iNO, 30/49 (61%) had >20% drop in PVR, 20% had >20% drop in mean pulmonary artery

pressure (mPAP) and PVR, and 8% had >10 mmHg decline in mPAP to mPAP < 40 with normal cardiac output. Patients on riociguat had less response to $O_2$ + iNO than patients on phosphodiesterase-5 inhibitors. Our findings shed light on the significant variability in vascular tone that is present in CTEPH, confirming that CTEPH represents a combination of mechanical obstruction and vasoconstriction that appears similar to that observed with Group 1 PAH. Additional study regarding whether results of acute vasodilator testing predict response to therapy and relate to prognosis is warranted.

**KEYWORDS**
catheterization, nitric oxide, pulmonary embolism, vasoreactivity

## INTRODUCTION

Elevation in pulmonary artery pressures can be driven by pulmonary vascular remodeling, thrombosis, vasoconstriction, high blood flow, elevation in left heart filling pressures, or by combinations of these factors. Guideline-directed acute vasoreactivity testing (AVT) with inhaled nitric oxide (iNO) during right heart catheterization is routinely performed in the treatment of naïve patients with idiopathic pulmonary arterial hypertension (IPAH) with the goal of identifying patients who may be candidates for long-term calcium channel blocker therapy. The frequency and significance of changes in hemodynamics with iNO during AVT in patients with chronic thromboembolic pulmonary hypertension (CTEPH) and in patients already on vasodilator therapy are less well characterized.

An acute vasoreactivity response (AVR) as defined by the robust response suggested for calcium channel blocker utilization in IPAH (a reduction of mean pulmonary artery pressure [mPAP] ≥ 10 mmHg to reach an absolute value of mPAP ≤40 mmHg with an increased or unchanged cardiac output [CO][1]) has been reported in 6-13% of CTEPH patients, a frequency similar to that observed in patients with PAH.[2] Compared to those with smaller decreases in mPAP, CTEPH patients having >10.4% decline in mPAP with iNO (24/62, 39%) had better outcomes following pulmonary thromboendarterectomy, raising the possibility that vasoreactivity testing may have clinical utility for understanding prognosis and guiding the management of CTEPH.

In the Pulmonary Vascular Disease Phenomics Study (PVDOMICS) we assessed AVT with oxygen alone ($O_2$) and oxygen plus nitric oxide ($O_2$ + iNO) in all World Symposium on Pulmonary Hypertension (WSPH) groups, including those with CTEPH. AVT was performed systematically in all patients with elevated mPAP (>20 mmHg) regardless of etiology or hemodynamic findings unless the patient was known to retain carbon dioxide with oxygen supplementation, had a right atrial pressure ≥14 mmHg, or a mean pulmonary artery wedge pressure (PAWP) ≥ 20 mmHg. This protocol-driven assessment of AVT provides an opportunity to examine vasoreactivity systematically in this understudied patient population of patients with pulmonary hypertension (PH).

We hypothesized that the majority of patients with CTEPH would demonstrate vasoreactivity and have a positive AVT in keeping with our understanding of CTEPH as a pulmonary vascular disease characterized by pulmonary vascular obstruction and vasoconstriction.

## METHODS

### Study cohort and vasoreactivity testing

Right heart catheterization, including vasodilator challenge with 100% oxygen ($O_2$) and 100% oxygen plus 40 PPM inhaled nitric oxide ($O_2$ + iNO) was performed. At baseline and 5 min following each intervention, we measured mean pulmonary artery pressure (mPAP), PAWP, and CO by thermodilution, with calculation of pulmonary vascular resistance (PVR). Details of PVDOMICS methodology, PVDOMICS Study Group members, core adjudication of hemodynamic measurements, and overall cohort characteristics are as previously reported.[3–5] The PVDOMICS study was approved by local institutional review boards and all patients provided written informed consent.

### Definitions of vasoreactivity

For the purposes of the analyses, we explored several definitions of vascular reactivity that have been reported previously:

a. Decline in mPAP by >10 mmHg to a value less than 40 mmHg with normal CO.[6,7]
b. Decline in both mPAP and PVR by >20%.[7,8]
c. Decline in PVR by >20%. This category is inclusive of those with and without >20% decline in mPAP.
d. Decline in PVR by >20% with less than 20% decline in mPAP (resistance-only responders). This category was included since sometimes decline in PVR can reflect a rise in wedge pressure or increase in CO that may have different implications than a concomitant decline in mPAP.

## Statistical analysis

We summarized the distribution of continuous measures with means and SDs or with medians and interquartile ranges, depending on skewness. We summarized categorical allotments using counts and percentages. We tested whether subject hemodynamic values changed from resting to the vasodilatory challenge phase using paired *t*-tests or Wilcoxon signed-rank tests, depending on data distribution. We compared measures between responders and non-responders using *T*-tests, Fisher's Exact tests, Wilcoxon rank-sum tests, and Pearson $\chi^2$ tests. We also performed a sensitivity analysis excluding those subjects having prior balloon pulmonary angioplasty or pulmonary endarterectomy given potential for impact of those procedures on vasoreactivity. Statistical power was assessed utilizing data from similar analysis of Lang and colleagues,[2] confirming adequacy of our cohort size for the analyses performed. Possible responder/nonresponder differences in time to first lung and/or heart transplant or all-cause mortality were summarized using Kaplan–Meier curves and formally tested using the Cox proportional hazards model. We used scaled Schoenfeld residuals to check the proportional hazards assumption.

All reported *p* values are two-sided without adjustment for multiple comparisons. Analyses were performed using SAS Studio software, release 3.7 (SAS Institute) and R (R Development Core Team).

# RESULTS

Fifty-six patients with CTEPH were enrolled in PVDOMICS and underwent right heart catheterization; 49 of these patients underwent vasodilator challenge during cardiac catheterization and are the subject of this report.

Characteristics of the study population are shown in Table 1. The majority of patients were prevalent cases (81.6%) and the median time from diagnosis was 1.1 years

**TABLE 1** Patient characteristics

| Factor | Total ($N = 49$) |
|---|---|
| Demographics and other clinical data | |
| Age (years) at enrollment | 57.2 ± 13.5 |
| Female | 31 (63.3) |
| Prevalent PH at enrollment | 40 (81.6) |
| Among prevalent subjects, years since PH diagnosis | 1.1 [0.58, 3.6] |
| WSPH Group 4 (pure) | 29 (59.2) |
| WSPH Mixed Group 4,1 | 2 (4.1) |
| WSPH Mixed Group 4,2 | 7 (14.3) |
| WSPH Mixed Group 4,3 | 10 (20.4) |
| WSPH Mixed Group 4,5 | 1 (2.0) |
| BMI ($kg/m^2$) | 32.1 ± 7.5 |
| Functional class[a] | |
| Class I | 1 (2.1) |
| Class II | 18 (37.5) |
| Class III | 28 (58.3) |
| Class IV | 1 (2.1) |
| 6MWD (m)[a] | 361.4 [273.7, 426.7] |
| NTproBNP (pg/ml)[a] | 184.1 [83.1, 607.5] |
| DLCO % predicted | 61.2 ± 19.0 |
| Room air: pulse oximetry $O_2$ saturation (%)[a] | 94.2 ± 3.5 |
| Room air: Pulse oximetry $O_2$ saturation <90[a] | 4 (8.9) |
| $SpO_2$ at end of 6 min. walk (%)[a] | 90.8 ± 5.2 |
| $SpO_2$ at end of 6 min. walk <90%[a] | 14 (33.3) |
| RHC, ECHO, MRI | |
| RHC capacitance (ml/bpm × mmHg)[a] | 2.4 ± 1.5 |
| ECHO: RV free wall strain (3 Segments) (%)[a] | −19.0 ± 5.5 |
| ECHO: TAPSE (cm)[a] | 1.9 ± 0.44 |
| ECHO: RV fractional shortening (%)[a] | 31.4 ± 10.5 |
| MRI: RVEF (%)[a] | 39.1 ± 11.5 |
| Treatment | |
| Prior pulmonary thromboendarterectomy | 13 (26.5) |
| Prior balloon pulmonary angioplasty | 3 (6.1) |
| No prior surgical intervention | 34 (69.4) |
| On anticoagulants—DOACS | 19 (38.8) |
| On anticoagulants—warfarin | 20 (40.8) |

(Continues)

**TABLE 1** (Continued)

| Factor | Total ($N = 49$) |
|---|---|
| On anticoagulants—heparin analogs | 12 (24.4) |
| On PH medication | 24 (49.0) |
| Soluble guanylate cyclase stimulator | 17 (34.7) |
| PDE5i | 6 (12.2) |
| Selexipag | 1 (2.0) |
| Currently using oxygen at rest | 12 (24.5) |
| Currently using oxygen at night | 20 (40.8) |
| Currently using oxygen during exertion | 16 (32.7) |

*Note*: Statistics presented as mean ± SD, median [P25, P75], *N* (column %).

Abbreviations: 6MWD, 6min walk distance; BMI, body mass index; ECHO, echocardiography; MRI, magnetic resonance imaging; PDE5i, phosphodiesterase-5 inhibitor; PH, pulmonary hypertension; RHC, right heart catheterization; RVEF, right ventricular ejection fraction; TAPSE, tricuspid annular plane systolic excursion; WSPH, World Symposium on Pulmonary Hypertension.

[a]Data not available for all subjects. Missing values: Functional class = 1; 6MWD (m) = 7; NTproBNP (pg/ml) = 1; RHC resting: pulse oximetry $O_2$ saturation (%) = 4; RHC resting: pulse oximetry $O_2$ saturation < 90 = 4; $SpO_2$ at end of 6 min walk (%) = 7; $SpO_2$ at end of 6 min walk < 90% = 7; DLCO % predicted = 5; RHC resting: capacitance (ml/bpm mmHg) = 13; ECHO: RV free wall strain (3 segments) (%) = 10; ECHO: TAPSE (cm) = 10; ECHO: RV fractional shortening (%) = 9; MRI: RVEF (%) = 13; use of $O_2$ during the night (Y/N) = 21.

(0.6, 3.6 years). More than half of the patients were WHO functional Class III at the time of study entry with a median 6 min walk distance of 361 m (274, 427 m). About half (49%) of the patients were on PH targeted therapy, most commonly riociguat ($n = 17$, 35%) or a phosphodiesterase-5 inhibitor (PDE5i) ($n = 8$, 16%) and six patients (12%) were receiving combined targeted therapy. Right ventricular function was mildly impaired and NTproBNP levels were relatively low (median NTproBNP 184.1 [83.1, 607.5] pg/ml). Thirteen patients (27%) had previously undergone pulmonary thromboendarterectomy, and 3 (6.1%) had prior balloon pulmonary angioplasty, one of whom had prior thromboendarterectomy.

Response to $O_2$ and $O_2$ + iNO in the overall cohort is shown in Table 2. Overall, $O_2$ alone had little effect on cardiopulmonary hemodynamics; however, $O_2$ + iNO resulted in reduction in mPAP by 4.3 ± 4.7 mmHg ($p < 0.0001$) with a 21% decline in PVR from 5.2 ± 2.9 to 4.1 ± 2.7 WU ($p < 0.0001$) in the study sample. There was no significant change in CO. Pulmonary artery capacitance improved.

mPAP and PVR at baseline and with the vasodilator challenges are shown for each subject in Figure 1a and b, respectively.

The number of patients who met the various definitions of vasoreactivity are shown in Table 3.

Though 14 (29%) patients had >20% drop in PVR with $O_2$, very few met the criteria for a positive response using the stricter definitions (Table 3). With $O_2$ + iNO, nearly two-thirds (61%) of patients had greater than 20% decline in PVR, while 10 (20%) had greater than 20% drop in both mPAP and PVR. All patients who had a drop in mPAP of >20% also had a drop in PVR of >20%. Only 4 (8%) patients had >10 mmHg decline in mPAP to a value <40 mmHg with normal CO. No significant difference in patient characteristics between those with and those without a drop in both mPAP and PVR > 20% were seen, though the small number of responders limits the power to detect differences (Supporting Information: -Table 1). We also looked for differences in oxygen saturation at rest and with 6 min walk, clinical utilization of oxygen, and DLCO between patients having greater than 20% reduction in PVR with $O_2$ or $O_2$ + iNO and those without such a response and did not detect differences, aside from slightly higher resting oxygen saturations in those responding to the challenges (Supporting Information: Table 2).

Patients on no PH therapy had slightly worse baseline hemodynamics than those on therapy. Median changes with $O_2$ + iNO in those not on PH therapy were not significantly different from those on PH therapy (Supporting Information: Tables 3a and 3b).

We performed a sensitivity analysis regarding robustness of our findings of vasodilator response by excluding subjects who had undergone prior balloon pulmonary angioplasty or pulmonary endarterectomy (Supporting Information: Table 4) and found very similar frequency of response. Previously, Lang and colleagues[2] found that PVR decreased by 105.4 ± 134.4 dyne s $cm^{-5}$ (15%) with $O_2$ + iNO among patients ($n = 44$) who did not undergo pulmonary endarterectomy.[2] The statistical power for replicating this result among the 34 like subjects in our cohort was 0.99 at $\alpha = 0.05$. Also, the probability that a replicated estimate would be in the opposite direction (Type S error) was zero and the degree to which the replicated estimate might exaggerate the magnitude of the true effect (Type M error) was estimated to be 0.5%.[9,10]

Results of the vasoreactivity testing with $O_2$ + iNO including separation by type of PH drug treatment are shown in Table 4. Only 1 of 17 (5.9%) of patients on riociguat had greater than 20% drop in both mPAP and PVR versus 4 of 6 (66.7%) of those on PDE5i ($p = 0.012$).

The response of those on PDE5i and those on soluble guanylate cyclase (sGC) stimulator therapy are shown in Tables 5a and 5b, respectively. Baseline mPAP and PVR were greater in the PDE5i group. There was greater reduction in both mPAP and PVR in the PDE5i group than in the sGC stimulator group (change in mPAP −9.5 ± 5.2 vs. −2.3 ± 3.0 mmHg, $p = 0.0023$; change in

**TABLE 2** Response to $O_2$ and $O_2$ + iNO in the overall cohort

| | Resting ($N = 49$) | $O_2$ ($N = 49$) | $O_2$ + iNO ($N = 49$) | Delta resting to $O_2$ + iNO ($N = 49$) | $p$ Value (resting vs. $O_2$ + iNO) |
|---|---|---|---|---|---|
| mPAP (mmHg) | 36.7 ± 11.8 | 34.6 ± 11.7 | 32.4 ± 11.3 | −4.3 ± 4.7 | <0.0001[a] |
| PAWP (mmHg) | 11.3 ± 4.7 | 11.9 ± 4.1 | 12.4 ± 4.5 | 1.1 ± 3.5 | 0.028[a] |
| CO (L/min) | 5.3 ± 1.6 | 5.1 ± 1.5 | 5.3 ± 1.5 | −0.01 ± 0.73 | 0.93[a] |
| PVR (WU) | 4.3 [3.1, 7.4] | 4.3 [2.6, 6.6] | 3.3 [2.3, 5.6] | −0.99 [−1.60, −0.26] | <0.0001[b] |
| | 5.2 ± 2.9 | 4.9 ± 3.1 | 4.1 ± 2.7 | −1.10 ± 1.07 | |
| Capacitance (ml/bpm mmHg) | 2.0 [1.3, 2.9] | 2.4 [1.4, 3.2] | 2.5 [1.7, 3.3] | 0.29 [0.03, 0.71] | <0.0001[b] |
| | 2.3 ± 1.4 | 2.4 ± 1.3 | 2.8 ± 1.6 | 0.45 ± 0.78 | |

*Note*: Statistics presented as mean ± SD, median [P25, P75].

Abbreviations: CO, cardiac output; iNO, inhaled nitric oxide; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance.

[a]Paired *t*-test.

[b]Wilcoxon signed-rank test.

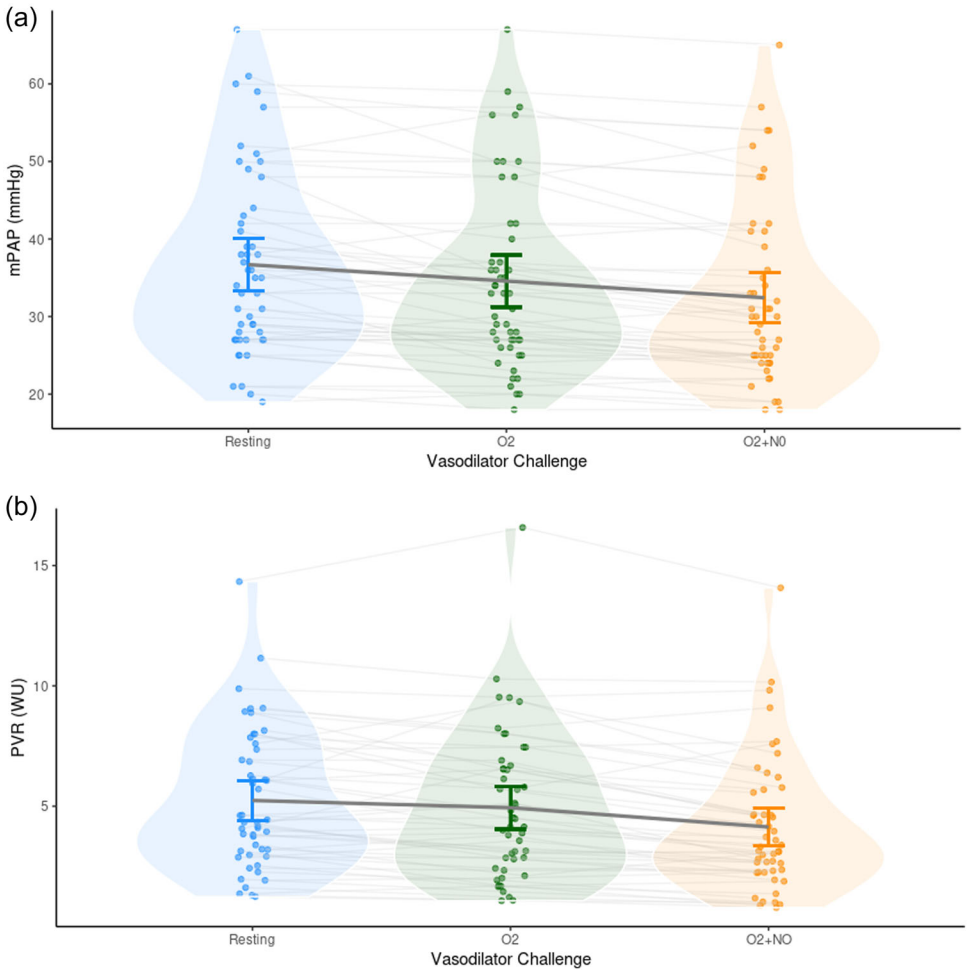


**FIGURE 1** (a) Mean pulmonary artery pressure at baseline, with $O_2$ and $O_2$ + iNO. $p$ Value <0.0001 between resting and $O_2$ + iNO phases. (b) Pulmonary vascular resistance at baseline, with $O_2$ and $O_2$ + iNO. $p$ Value <0.0001 between resting and $O_2$ + iNO phases. iNO, inhaled nitric oxide; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance.

**TABLE 3** Response to oxygen and oxygen plus inhaled nitric oxide by vasoreactivity definition

| Factor | $O_2$ ($N = 49$) | | $O_2$ + iNO ($N = 49$) | |
|---|---|---|---|---|
| | *N* missing | *N* meeting definition | *N* missing | *N* meeting definition |
| >20% drop in PVR | 1 | 14 (29.2) | 0 | 30 (61.2) |
| >20% drop in both mPAP and PVR | 1 | 1 (2.1) | 0 | 10 (20.4) |
| >10 mmHg drop in mPAP to <40 with normal CO | 0 | 1 (2.0) | 0 | 4 (8.2) |

*Note*: Statistics presented as *N* (column %).

Abbreviations: CO, cardiac output; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance.

**TABLE 4** Vasoreactivity response to combined oxygen plus nitric oxide (no missing data)

| Factor | Overall cohort ($N = 49$) | No PH drugs ($N = 25$) | sGC stimulator ($N = 17$) | PDE5i ($N = 6$) | Other PH med ($N = 6$) | Combination PH therapy ($N = 5$) | Prior endarterectomy ($N = 13$) | Prior BPA ($N = 3$) |
|---|---|---|---|---|---|---|---|---|
| >20% drop in PVR | 30 (61.2) | 15 (60.0) | 9 (52.9) | 6 (100) | 2 (33.3) | 2(40) | 8 (61.5) | 3 (100.0) |
| >20% drop in Both mPAP and PVR | 10 (20.4) | 5 (20.0) | 1 (5.9) | 4 (66.7) | 0 | 0 | 1 (7.7) | 0 |
| >10 mm drop in mPAP to <40 with normal CO | 4 (8.2) | 2 (8.0) | 0 | 2 (33.3) | 0 | 0 | 0 | 0 |

*Note*: Statistics presented as *N* (column %).

Abbreviations: BPA, balloon pulmonary angioplasty; CO, cardiac output; mPAP, mean pulmonary artery pressure; PDE5i, phosphodiesterase-5 inhibitor; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; sGC, soluble guanylate cyclase.

**TABLE 5a** Hemodynamic response to oxygen and oxygen plus nitric oxide (PDE5i)

| | Resting ($N = 6$) | $O_2$ ($N = 6$) | $O_2$ + iNO ($N = 6$) | Delta resting to $O_2$ + iNO ($N = 6$) | *p* Value (resting vs. $O_2$ + iNO) |
|---|---|---|---|---|---|
| mPAP (mmHg) | 42.3 ± 11.8 | 37.3 ± 13.5 | 32.8 ± 10.6 | −9.5 ± 5.2 | 0.0068[a] |
| PAWP (mm Hg) | 13.3 ± 4.6 | 13.3 ± 5.5 | 13.8 ± 5.2 | 0.50 ± 2.3 | 0.61[a] |
| CO (L/min) | 5.1 ± 0.90 | 4.6 ± 0.69 | 5.1 ± 0.52 | −0.04 ± 0.64 | 0.87[a] |
| PVR (WU) | 7.1 [3.1, 8.1] | 6.8 [1.7, 7.5] | 4.6 [0.91, 5.8] | −2.3 [−2.5, −1.6] | 0.031[b] |
| | 6.0 ± 2.9 | 5.3 ± 3.0 | 3.9 ± 2.4 | −2.1 ± 0.94 | |

*Note*: Statistics presented as mean ± SD, median [P25, P75].

Abbreviations: CO, cardiac output; iNO, inhaled nitric oxide; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance.

[a]Paired *t*-test.

[b]Wilcoxon signed-rank test.

median PVR −2.3 WU [−2.5, −1.6] vs. −0.51 WU [−1.2, −0.21], $p = 0.0022$), respectively.

We also examined patients ($n = 20$) who had >20% drop in PVR with less than 20% drop in mPAP. Hemodynamics of this group are shown in Supporting Information: Table 5. With the $O_2$ + iNO challenge, the mean decline in PVR of −1.65 ± 0.87 WU was driven by a combination of a decline in mPAP by −3.80 ± 1.99 mmHg and a rise in PCW of 2.65 ± 2.87 mmHg.

## Transplant-free survival

Our CTEPH cohort had follow-up for 33.9 ± 13.2 months. No patients received a heart and/or lung transplant during follow-up. Twelve of the 49 patients died (overall mortality [24.4%]). Nine of 39 nonresponders died (median survival time: 42.2 months) and 3 of 10 responders died (median survival could not be calculated). Survival did not differ between the

**TABLE 5b** Hemodynamic response to oxygen and oxygen plus nitric oxide (sGC stimulator)

| Factor | Resting ($N = 17$) | $O_2$ ($N = 17$) | $O_2$ + iNO ($N = 17$) | Delta resting to $O_2$ + iNO ($N = 17$) | *p* Value (resting vs. $O_2$ + iNO) |
|---|---|---|---|---|---|
| mPAP (mmHg) | 32.2 ± 10.7 | 31.0 ± 10.9 | 29.9 ± 11.4 | −2.29 ± 3.00 | 0.0061[a] |
| PAWP (mm Hg) | 10.8 ± 4.2 | 12.2 ± 4.2 | 12.9 ± 5.2 | 2.18 ± 3.68 | 0.027[a] |
| CO (L/min) | 5.8 ± 2.3 | 5.5 ± 2.1 | 5.7 ± 2.0 | −0.10 ± 0.95 | 0.67[a] |
| PVR (WU) | 3.8 [2.3, 5.9] | 3.1 [1.9, 5.1] | 2.8 [1.9, 3.7] | −0.51 [−1.20, −0.21] | 0.021[b] |
| | 4.1 ± 2.4 | 3.9 ± 2.6 | 3.4 ± 2.4 | −0.73 ± 0.83 | |

*Note*: Statistics presented as mean ± SD, median [P25, P75].

Abbreviations: CO, cardiac output; iNO, inhaled nitric oxide; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance.

[a]Paired *t*-test.

[b]Wilcoxon signed-rank test.

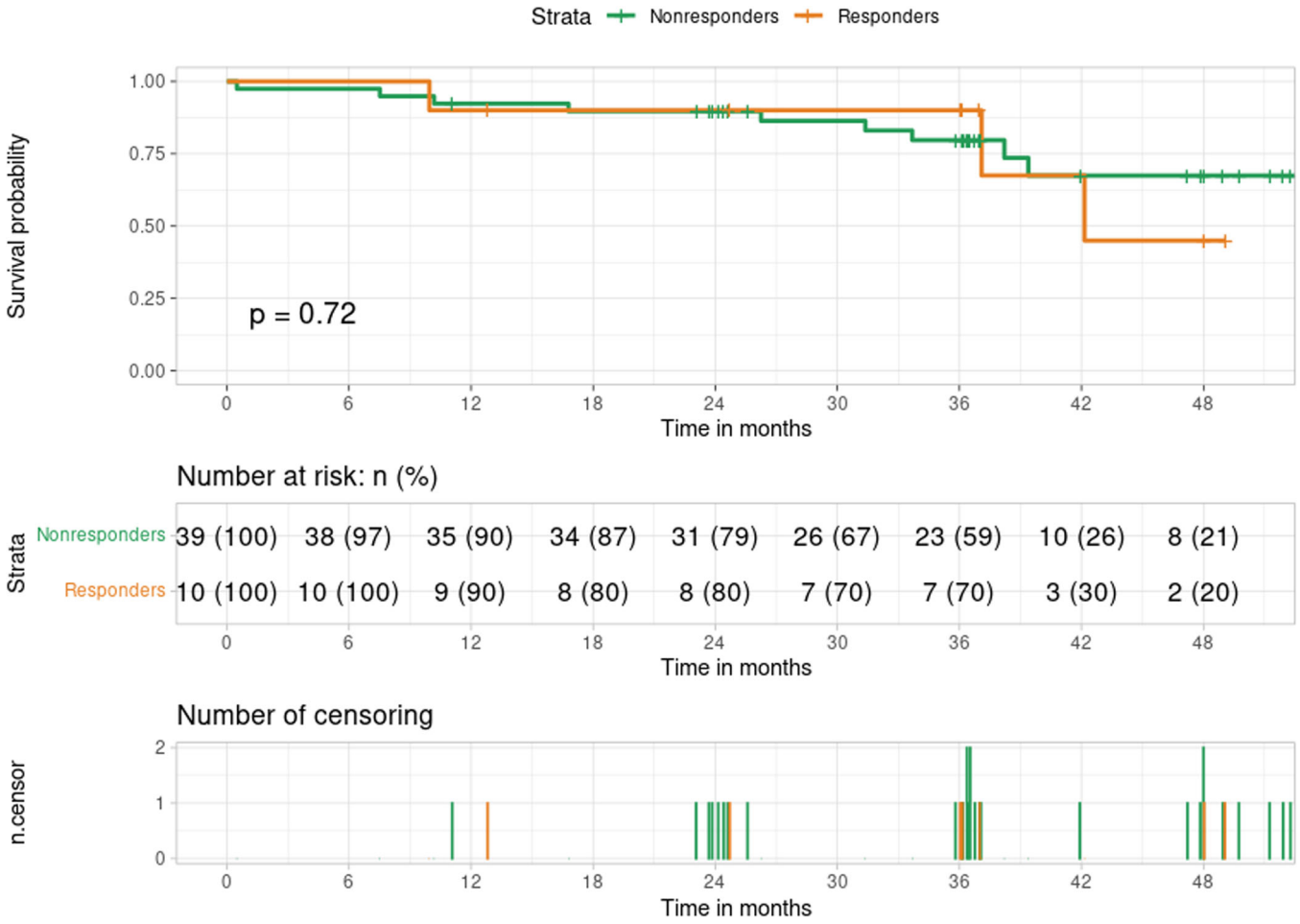


**FIGURE 2** Transplant-free survival stratified by acute vasodilator test responsiveness

two groups. The risk of death for responders as compared to nonresponders was 1.27 (95% CI: 0.34–4.69, Figure 2). Causes of death included: Cardiac arrest ($n = 1$), right heart failure ($n = 2$ including one with right-sided prosthetic valve endocarditis), unwitnessed death within 24 h of last seen alive in a patient with known very severe PH ($n = 1$), intraoperative death during thromboendarterectomy ($n = 1$), GI bleed ($n = 1$), traumatic brain injury ($n = 1$), sepsis ($n = 1$), and unknown ($n = 4$).

## DISCUSSION

Since the usual goal of vasoreactivity testing is to define suitability for a trial of calcium channel blocker therapy in Group 1 PAH, which is not recommended for the treatment of CTEPH, AVT in CTEPH is rarely performed. Prior studies of vasodilator testing in CTEPH also did not test the acute effects of supplemental oxygen, which is performed infrequently and is typically reserved for patients with congenital heart disease and patients with resting hypoxemia.

Our interest was broader, seeking to define the extent to which the pulmonary vasculature in CTEPH can be modulated with both oxygen and iNO during AVT, which speaks to the underlying pathophysiology and possibly insights into the management approach to these patients. Oxygen challenges are typically utilized either in patients with congenital heart disease or others with resting hypoxemia who may have hypoxemia as one mechanism of pulmonary arterial vasoconstriction, since hypoxemia is a potent pulmonary vasoconstrictor. Oxygen challenges are not typically performed in other forms of pulmonary hypertension. CTEPH is characterized by varying degrees of mechanical obstruction of the conduit vessels, combined with varying degrees of vasoconstriction and structural changes (remodeling) thought to be mediated by high pressure and flow of blood in the non-obstructed pulmonary arterial and arteriolar vessels, leading to endothelial dysfunction, vasodilator/vasoconstrictor imbalance, regional V/Q mismatch, and in some patients, hypoxemia at rest or with exertion. The pathologic changes seen in these pulmonary vessels are reminiscent of those seen in patients with idiopathic PAH.[11] We found that AVT is safe in CTEPH, with the proviso that we did not perform AVT if PAWP ≥ 20 mmHg.

### Acute response to 100% oxygen

We found that 14 (29%) patients had >20% drop in PVR with $O_2$. We were not able to identify any predictors of this response. Only one patient had a drop in mPAP and PVR by >20% with $O_2$ challenge alone. This is not surprising since in the absence of major hypoxemia it would not necessarily be expected that oxygen would serve as a significant pulmonary vasodilator. The finding that 29% of patients had >20% drop in PVR with oxygen is of interest. Administration of oxygen during exercise training in patients with CTEPH and also PAH has been shown to improve exercise performance even in the absence of resting hypoxemia (hyperoxic exercise training).[12] The mechanism of this benefit is felt to reflect improved arterial, muscular and cerebral oxygenation and reduced sympathetic tone.[13] Our finding that oxygen results in acute decline in PVR in some patients with CTEPH suggests potential for additional studies further examining use of oxygen therapy in CTEPH, including exploration of use of oxygen during exercise training sessions in CTEPH.

### Acute response to oxygen plus nitric oxide

Pulmonary endarterectomy is the treatment of choice for operable patients with CTEPH. Options for patients with inoperable or residual CTEPH include balloon pulmonary angioplasty and/or pulmonary vasodilator therapy. Phosphodiesterase 5 inhibitors have been utilized based on case series suggesting benefit.[14] However, there were no vasodilators specifically approved for treatment of CTEPH until 2013. The soluble guanylate cyclase stimulator riociguat is the only FDA-approved PH therapy for inoperable or residual CTEPH after endarterectomy. Riociguat has been shown to improve functional class, 6 min walk, mPAP, PVR, CI, and NTproBNP levels[15] in CTEPH patients who are inoperable and those who have postoperative residual PAH. Since it works via the nitric oxide pathway, it seems intuitive that acute response to inhaled nitric oxide might have some relationship to the chronic response to riociguat. The same could be said for PDE5 inhibitors, but they work by inhibiting breakdown of cGMP, so if the nitric oxide input signaling is deficient, PDE5 inhibition may not maximally leverage the nitric oxide pathway. Alternatively, riociguat directly stimulates soluble guanylate cyclase, and amplifies sensitivity of soluble guanylate cyclase to nitric oxide, so it may leverage the nitric oxide signaling pathway more effectively. Our finding of greater residual nitric oxide vasoreactivity in patients on PDE5i compared to those on riociguat further supports this concept. The RESPITE and REPLACE studies suggesting hemodynamic and clinical benefit of converting Group 1 PAH patients from PDE5i to riociguat also align with this concept.[16–18] Nonetheless 9 of 17 (53%) of the patients on riociguat still had >20% decline in PVR with $O_2$ + iNO, suggesting some room for additional vasodilation. These findings raise the question of whether AVT with iNO may have a role in CTEPH patients both in predicting outcome (similar to Group 1) and to define a group who should be more aggressively treated with PAH therapies targeting the nitric oxide pathway and other pathways.

### Response in patients without prior balloon pulmonary angioplasty or thromboendarterectomy

Our finding of similar frequency of AVT response in patients with or without prior CTEPH intervention is of interest, indicating commonality of vasomotor responses in disparate CTEPH circumstances.

## Relationship of current findings to prior published experience of vasoreactivity testing

Our findings in the context of prior research are shown in Table 6.

Rich et al.[19] reported acute hemodynamic response to vasodilators in 23 patients with idiopathic (then known as primary) pulmonary hypertension. Patients with >20% decline in PVR were found to have better survival regardless of treatment than those without such a response. AVT in that study was performed with nifedipine or hydralazine, which often increased CO, and decline in mPAP though studied was not specifically used as a metric of responsiveness.

In a study of 47 primary pulmonary hypertension patients tested acutely with nifedipine or diltiazem, 15 (32%) had >20% reduction in mPAP and PVR, while 19 (40%) had >20% reduction in PVR with less than 20% decrease in mPAP.[8] Accordingly, 72% had >20% decline in PVR, which is close to our finding of 61% (30/49).

Sitbon et al.[7] utilized intravenous epoprostenol for AVT until 1994, and subsequently inhaled nitric oxide because of its greater safety and ease of use. In their study of 557 idiopathic PAH patients, 12.6% had a drop of >20% for both mPAP and PVR in response to inhaled NO, less than our 20.4%. Since this definition of response was felt to be insufficiently specific for identification of Group 1 patients who would respond long term to calcium channel blockers (only 54% of patients meeting

**TABLE 6** Summary of acute vasodilator studies

| References | Population | Vasodilator | 20% decline PVR | 20% decline mPAP and PVR | 20% decline mPAP, PVR to mPAP <40 |
|---|---|---|---|---|---|
| This study | CTEPH ($n = 49$) | $O_2$ | 29% | 2% | 2% |
| This study | CTEPH ($n = 49$) | $O_2$ + iNO | 61% | 20% | 8% |
| Xu et al.[23] | CTEPH ($n = 175$) | Inh iloprost | | | 14% |
| Lang and colleagues[2] | CTEPH ($n = 101$) | iNO | | | 13% |
| Rich et al.[8] | IPAH ($n = 47$) | Nifedipine, hydralazine | 72% | 32% | |
| Sitbon et al.[7] | IPAH ($n = 557$) | EPO or iNO | | 12.6% | |
| | | | | **20% decline mPAP** | |
| Ulrich et al.[24] | CTEPH ($n = 22$) | iNO | 46% | 9% | 6% |
| | PAH ($n = 35$) | iNO | 37% | 6% | 6% |
| | | | | **20% decline mPAP** | |
| Ulrich et al.[24] | CTEPH ($n = 22$) | Iloprost | 41% | 18% | 5% |
| | PAH ($n = 35$) | Iloprost | 52% | 23% | 17% |
| | | | | **20% decline mPAP and TPR** | |
| Montani et al.[28] | Group 1 non I,H PAH ($n = 663$) | Epo or iNO | | 10%–13% | 4.4% |
| | | | ≥30% decline PVR | **≥12% decline mPAP** | |
| Malhotra et al.[22] | Group 1 PAH | $O_2$ + iNO | 51% | 50% | 9% |

Abbreviations: CTEPH, chronic thromboembolic pulmonary hypertension; iNO, inhaled nitric oxide; mPAP, mean pulmonary artery pressure; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance.

this definition had long-term response), a stricter definition was formulated requiring a drop in mPAP by >10 mmHg to a value <40 mmHg with normal CO that is referenced in subsequent treatment recommendations.[1,20,21] Four (8.2%) of our patients met the latter definition.

Malhotra et al.[22] examined the relationship of change in PVR and change in mPAP with acute NO challenge to outcome in patients with PAH. They found that 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 for every 10% reduction in baseline mPAP with vasodilator there was a reduction in mortality by a factor of 0.60 (95% CI: 0.43–0.83, $p = 0.002$).

Among 175 patients with CTEPH in the Xu study, an acute vasoreactivity assessment with inhaled iloprost demonstrated that 25 (14%) had >10 mmHg decline in mPAP to a value <40 mmHg with normal or increased CO.[23] In 101 CTEPH patients tested with inhaled nitric oxide, Lang and colleagues[2] found an overall reduction of mPAP of 8.8 ± 12.6% ($p < 0.0001$) and PVR 16.1 ± 18.1%; $p < 0.0001$). They found that 12.9% of CTEPH patients tested with inhaled nitric oxide met the strict definition. They also found that a decline in mPAP >10.4% with acute vasodilator testing was associated with better survival following surgical thromboendarterectomy.

Ulrich et al. administered both inhaled nitric oxide and iloprost in patients with PAH and in patients with CTEPH. They found similar acute changes in mPAP and PVR in the PAH and CTEPH patients.[24] No relationship of the acute response to the subsequent clinical response (6 min walk distance and functional class) to inhaled iloprost was seen, but there were only 20 patients treated with long-term iloprost, limiting power to detect a relationship.

## Relevance of inhaled nitric oxide testing in CTEPH

For patients with CTEPH who meet previously established criteria for use of calcium channel blockers in Group 1 PAH, the question arises whether they might respond favorably to calcium channel blockers. However, concern has been raised about potential for aggravation of ventilation/perfusion mismatch.[24] Enthusiasm for consideration of calcium channel blocker therapy in CTEPH has been low[25] Specific peripheral blood RNA expression patterns can identify patients with acute vasodilator-responsive PAH[26]; it would be of interest to examine whether these patterns are also seen in CTEPH and other forms of pulmonary hypertension with acute vasodilator responsiveness, suggesting commonality of physiologic processes. Overall survival in our cohort of 75.4% is lower than the 3-year survival of 89% for operated patients and similar to the 70% 3-year survival for nonoperated patients in a large international cohort.[27] This suggests that CTEPH patients entered into PVDOMICS represent a relatively high-risk cohort. We did not observe a difference in outcome based upon vasodilator responsiveness. This may reflect that this is predominantly a prevalent population and those patients already on riociguat were usually nonresponders, potentially since the nitric oxide pathway was already well treated, and their hemodynamics in this context were less abnormal than the responders. Causes of death were quite varied but often cardiovascular in nature.

## STUDY LIMITATIONS

In our study, AVT was protocol driven so the iNO challenge was performed on the background of the oxygen challenge and we do not have results from an isolated iNO challenge. The overall cohort and the subcohorts of patients on PDE5i or riociguat are small and predominantly prevalent, so observations about relative acute vasoreactivity must be considered in that context. Further, only 10 of our patients had a previous PTE and/or balloon pulmonary angioplasty which reflects that some of these data are acquired after an intervention for CTEPH. Our database does not include information regarding drug doses, so it is unknown whether patients were at peak approved dose of medication, but presumably they would have been titrated to the highest tolerated dose. Omic data regarding OMIC prediction of AVT responsiveness in CTEPH from PVDOMICS are not yet available

## CONCLUSIONS

By performing protocol-driven AVT in patients with CTEPH enrolled in PVDOMICS, we found that 61% of patients have over a 20% drop in PVR with AVT, 20% have >20% drop in mPAP and PVR, and 8% have >10 mmHg decline in mPAP to mPAP < 40 with normal CO, similar to the frequencies of these responses observed in patients with idiopathic PAH. This includes patients with prior pulmonary thromboendarterectomy and those on PDE5i or other PH therapy. Patients on riociguat have some but relatively less acute responsiveness, suggesting that riociguat is already impacting the nitric oxide pathway sufficiently that additional response to nitric oxide is limited. Our findings shed light on the

significant dysregulation in vascular tone that is present in CTEPH, confirming that CTEPH represents a combination of mechanical obstruction and vascular dysfunction that appears similar to that observed with Group 1. Additional studies regarding whether results of acute vasodilator testing predict responses to chronic therapy and relate to prognosis are warranted.

## AUTHOR CONTRIBUTIONS

**Robert P. Frantz**, **Jane A. Leopold**, **Paul M. Hassoun**, **Anna R. Hemnes**, **Evelyn M. Horn**, **Erika B. Rosenzweig**: Conception and design; data collection; data analysis and interpretation; drafting the article; critical revision of the article; final approval of the article. **Stephen C. Mathai**, **Franz P. Rischard**, **W.h. Wilson Tang**, **Margaret M. Park**: Conception and design; data collection; data analysis and interpretation; critical revision of the article; final approval of the article. **A. Brett Larive**: Conception and design; data analysis and interpretation; drafting the article; critical revision of the article; final approval of the article. **Nicholas S. Hill**: Conception and design; data analysis and interpretation; drafting the article; critical revision of the article; final approval of the article.

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## CONFLICTS OF INTEREST

Anna R. Hemnes has served as a consultant for Bayer, United Therapeutics, Janssen, GossamerBio, and Tenax Therapeutics; holds stock in Tenax Therapeutics; and has received grants from the National Institutes of Health, CMREF, and Imara. Erika B. Rosenzweig has received consulting fees from Acceleron for a scientific advisory board meeting; and her institution receives grant support from Bayer, United Therapeutics, Janssen, and SonVie. Robert P. Frantz has consulting, steering committee, and advisory board relationships with Altavant Sciences, Bayer, Gossamer Bio, Janssen, Shouti, France Foundation, IQVIA, Tenax Therapeutics, UpToDate, and United Therapeutics. Paul M. Hassoun has served as scientific advisor for Merck Sharp & Dohme, an activity unrelated to the current work. Nicholas S. Hill has received research grants for Acceleron, Aerovate. Altavant, Gossamer. Liquidia, Merck, and United Therapeutics; and has served on advisory boards for Acceleron, Aerovate, Altavant, Gossamer, and Liquidia. Actelion Sciences, and Tenax Therapeutics; and has U.S. Patent#9,605,047, Patent pending PCT/US2019/059890, Patent application 2021/133937. Stephen C. Mathai has served as a consultant for Acceleron, Actelion Sciences, Bayer, and United Therapeutics. Margaret M. Park has served on the Speakers Bureau of Lantheus Medical Imaging (Definity contrast). Franz P. Rischard has consulting relationships with Acceleron and United Therapeutics; is on a Steering Committee for Acceleron; and receives research support from Ismed, United Therapeutics, Bayer, Acceleron, Janssen, and AADI. Evelyn M. Horn has served on the Data and Safety Monitoring Board of AADi Biosciences and SoniVie; has served on the Clinical Events Committee for V-wave; and has served as a consultant for Biotronik. The remaining authors declare no conflicts of interest.

## ETHICS STATEMENT

The PVDOMICS study was approved by local institutional review boards and all patients provided written informed consent. An independent OSMB oversaw study conduct.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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