# Acute Vasoreactivity Testing during Cardiac Catheterization of Neonates with Bronchopulmonary Dysplasia-Associated Pulmonary Hypertension

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**Objectives** To assess whether better baseline pulmonary hemodynamics or positive acute vasoreactivity testing (AVT) during cardiac catheterization are associated with improved outcomes in infants with bronchopulmonary dysplasia (BPD) and pulmonary hypertension (PH).

**Study design** This retrospective, single-center study included 26 premature neonates with BPD who underwent catheterization to evaluate PH. AVT was assessed with exposure to 100% fractional inspired oxygen with or without inhaled nitric oxide. AVT was positive if the patient met the Barst criteria or increased shunt volume and decreased pulmonary vascular resistance index by >50%.

**Results** At baseline, the median pulmonary artery mean pressure was 29 mm Hg (IQR, 24-35) and the pulmonary vascular resistance index was 5.3 units*$m^2$ (IQR, 3.5-6.9). Nine patients (35%) had a positive AVT response, which was associated with a decreased risk of death or tracheostomy by 2-year follow-up (hazard ratio, 0.15; $P$ = .02). Baseline pulmonary hemodynamics and the presence of left ventricular diastolic dysfunction were not associated with late outcomes in this cohort.

**Conclusions** We found that 35% of infants with BPD who underwent catheterization had positive AVT and that a positive response was associated with better long-term outcomes than nonresponders. AVT better distinguishes higher from lower risk PH in infants with BPD than baseline pulmonary hemodynamics. AVT may aid in the assessment of disease severity and management of BPD-associated PH. *(J Pediatr 2019;208:127-33)*.

Pulmonary hypertension (PH) occurs in roughly 15% of extremely preterm infants, with prevalence as high as 25% of infants with severe bronchopulmonary dysplasia (BPD).[1,2] PH is linked with high mortality, ranging from 26% to 38% in participants, and is strongly associated with severe and sustained PH beyond 4-6 months of age.[1,3,4] Although interdisciplinary consensus recommendations for care have been described, data supporting optimal strategies to diagnose and manage BPD-associated infants with PH remain limited.[5,6]

Current recommendations suggest a central role for echocardiography to make the diagnosis of BPD-associated PH and for providing longitudinal assessments of PH, including the response to therapy.[5] However, echocardiography may not accurately identify the presence or severity of PH as confirmed by subsequent cardiac catheterization.[7] In addition, echocardiography alone may be insufficient to identify associated cardiovascular problems in infants with BPD.

Cardiac catheterization is considered the gold standard for the accurate assessment of PH in children and adults through direct measurement of pulmonary hemodynamics including pulmonary artery (PA) pressure and pulmonary vascular resistance index (PVRi).[6,8] However, the role of cardiac catheterization in the evaluation and management of BPD-associated PH remains controversial.[4,5,7,9,10] In past studies of infants with BPD, cardiac catheterization has been useful for identifying severity of PH and for assessment of contributions of anatomic shunts, left ventricular (LV) diastolic dysfunction, aortopulmonary collaterals, and pulmonary vein stenosis.[11] However, patients must be carefully selected for catheterization because the procedure is invasive and significant complications have been reported in children, especially those with PH.[12-16]

Baseline hemodynamics and acute responsiveness to vasodilator stimuli through acute vasoreactivity testing (AVT) can predict the risk of adverse clinical outcomes and has become a standard approach in assessing participants with PH.[6,8,17] In patients with idiopathic pulmonary arterial hypertension, positive AVT responses during brief exposure to vasodilators during cardiac catheterization

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|---|---|
| BPD | Bronchopulmonary dysplasia |
| AVT | Acute vasoreactivity testing |
| $FiO_2$ | Fractional inspired oxygen |
| LV | Left ventricular |
| PA | Pulmonary artery |
| PH | Pulmonary hypertension |
| PVRi | Pulmonary vascular resistance index |

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can identify those participants who have more favorable long-term outcomes and can be treated successfully with calcium channel blocker therapy.[11,17-21] However, whether positive AVT carries a similar prognostic value in BPD-associated PH has yet to be determined. Therefore, the purpose of this study was to evaluate baseline pulmonary hemodynamics during cardiac catheterization and the results of AVT in infants with BPD and PH, and to determine whether these indices are associated with clinical outcomes. We hypothesized that the basal hemodynamics and the results of AVT would help to identify infants with BPD and PH who are at greatest risk for poor clinical outcomes.

## Methods

This study was reviewed and approved by the Colorado Multiple Institution Review Board. Participants were identified retrospectively by query of the Children's Hospital Colorado cardiac catheterization database (PedCath, Scientific Software Solutions, Charlottesville, Virginia) and the electronic medical record (Epic Systems, Verona, Wisconsin) using the i2b2 search tool (available: i2b2.org). Participants admitted between 2009 and 2017 were included if they were born prematurely (gestational age of <36 weeks), had a diagnosis of BPD, and underwent cardiac catheterization during their initial admission to the neonatal intensive care unit. The primary clinical care team involved with each patient's care determined selection for cardiac catheterization. Indications generally were to characterize pulmonary hemodynamics and define potential contributing factors such as the impact of shunt lesions (eg, patent ductus arteriosus, ventricular septal defect, atrial septal defect), LV diastolic dysfunction, pulmonary vein stenosis, and aortopulmonary collaterals owing to the failure to improve PH as assessed by other clinical parameters.

All patients in this study had a diagnosis of PH based on echocardiography results that included increased tricuspid regurgitation jet velocity, systolic interventricular septal flattening, right ventricular dilation or hypertrophy, or low-velocity systemic-to-pulmonary shunt. If a patient had multiple catheterizations during their admission to the neonatal intensive care unit, only results from the first procedure were included. Patients with significant comorbid structural heart disease (eg, Tetralogy of Fallot, single ventricle, ductal-dependent anatomy) were excluded. However, those with simple shunt lesions (atrial or ventricular septal defects or patent arterial ducts) were included.

We recorded the clinical, vital, and demographic data from the electronic medical record for all participants. Results from the most recent echocardiogram before cardiac catheterization were extracted and aggregated for analysis. One investigator reviewed the clinical documentation from the weeks leading up to and after cardiac catheterization to identify complications and changes in clinical management attributable to the catheter procedure.

Pediatric cardiac interventionalists performed all catheterizations by standard procedures based on clinical standards of care.[5,11,22] Anesthesia was provided by a pediatric cardiac anesthesiologist with expertise in neonatal airway care and hemodynamic monitoring. Before obtaining hemodynamic values, the patient was kept well-oxygenated and ventilated with an arterial pH between 7.35 and 7.45, and pulse oximetry saturations of >92% throughout the procedure. Baseline pulmonary and systemic hemodynamics were measured via standard right heart catheterization.

Total pulmonary blood flow and total systemic blood flow were calculated based on the Fick principle (using $PO_2$ measurements when appropriate) with assumed oxygen consumption based on age and heart rate and were indexed to body surface area. The PVRi was calculated as the ratio of the transpulmonary gradient (mean PA pressure minus PA wedge pressure) to total pulmonary blood flow, and adjusted for body surface area. The systemic vascular resistance was calculated as the ratio of the systemic transcapillary gradient (mean systemic artery pressure minus central venous pressure) to the total systemic blood flow and then indexed to body surface area (indexed systemic vascular resistance). PH was defined by the measurement of a mean PA pressure of ≥25 mm Hg and a calculated PVRi of >3 Woods units*$m^2$.[6,23]

After obtaining baseline hemodynamic measurements, all participants were treated with fractional inspired oxygen ($FiO_2$) of 1.00 to assess the acute vasodilator response. Inhaled nitric oxide (range, 20-40 ppm) was also administered along with high $FiO_2$ in 16 patients (62%). After ≥10 minutes of combined drug and high $FiO_2$ administration, hemodynamic measurements (including $PO_2$) were repeated.

For those without a systemic-to-pulmonary shunt, the Barst criteria were used to define positive AVT, which include a decrease in the mean PA pressure of >20%, an increase or no change in the total systemic blood flow, and a decrease or no change in the ratio of the PVRi to the indexed systemic vascular resistance.[24] For those with a significant systemic-to-pulmonary shunt, we considered AVT positive if participants demonstrated at least a 50% increase in shunt volume and a 50% decrease in PVRi.

### Statistical Analyses

Analyses were performed in JMP (version 13.1 or higher; SAS Institute, Cary, North Carolina). Variables were checked for the distributional assumption of normality using normal plots, in addition to Kolmogorov-Smirnov and Shapiro Wilks tests. All normally distributed variables were reported as mean ± SD or as median with corresponding IQRs. Demographic and clinical characteristics between groups were compared using a Student $t$ test for normally distributed continuous variables, Mann-Whitney test was used for non-normally distributed variables, and $\chi^2$ for categorical variables. All patients were subjected to Cox proportional hazards modeling and Kaplan-Meier survival analysis to assess the prognostic value of catheterization data for selected clinical outcomes. A combined clinical outcome of death or

tracheostomy within 2 years was selected for the primary analysis. Participants without a clinical event were censored from the analysis at the time of last known follow-up or 2 years after catheterization, whichever was first.

## Results

Twenty-six participants met study inclusion criteria and were included in the analysis. Comprehensive demographics and clinical characteristics are described in the Table. The median gestational age and birth weight were 26 weeks and 580 g, respectively. The age at catheterization was at a median of 156 days (IQR, 112-180 days). The study population had a higher incidence of pregnancies complicated by intrauterine growth restriction (46%) and preeclampsia (35%) than chorioamnionitis (0%), substance abuse exposure (8%), and oligohydramnios (12%). Indications for catheterization included recurrent cyanotic episodes (15%), PH worsening by serial echocardiograms (46%), the need to clarify pulmonary hemodynamics for clinical decision-making (35%), and concerns about potential postcapillary obstruction (LV diastolic dysfunction or pulmonary vein stenosis; 23%). At the time of catheterization, 38% of participants were being treated with mechanical ventilation, 46% were already receiving a targeted PH therapy, such as inhaled nitric oxide or sildenafil, and 77% were receiving diuretics. Five participants (19%) required tracheostomy after catheterization, and 6 participants died (23%). There was no significant correlation noted between the year of catheterization and tracheostomy or death. Six participants were censored before 2 years after catheterization (median, 227 days; IQR, 123-353 days), 3 in the positive AVT group and 3 in the negative AVT group.

Ten participants were able to tolerate baseline measurements without supplemental oxygen ($FiO_2$ of 21%), and 16 required supplemental oxygen ($FiO_2$ range of 23%-55%). Baseline hemodynamic measurements are summarized in the Table. The mean PA pressure was 29 mm Hg (median; IQR, 24-35) and the ratio of systolic PA to systemic arterial pressure was 68%. The median PVRi was 5.3 Woods units*$m^2$ (IQR, 3.5-6.9) and 31% of patients had evidence of increased LV end-diastolic pressure (>10 mm Hg), suggesting LV diastolic dysfunction. Angiographic evidence of pulmonary vein stenosis was found in 7 patients (27%). PA angiography was performed in 19 patients. No patients were found to have significant pulmonary arteriovenous malformations. Angiography of the aorta was performed in 4 patients and none were found to have large aortopulmonary collateral arteries. Six patients had a therapeutic intervention performed at the time of catheterization including pulmonary vein angioplasty (4 participants), atrial septal defect closure (1 participant), and ductus arteriosus closure (1 participant). Two interventions were performed on participants in the reactive group (1 pulmonary vein angioplasty and 1 patent ductus arteriosus closure), and 4 interventions were performed on participants in the nonreactive group (22% vs 25%; $P = .87$). There was no significant association between having an intervention performed during catheterization and meeting the combined outcome of tracheostomy or death ($P = .37$).

Independent of the results of cardiac catheterization, participants were classified by the most recent echocardiogram as having mild, moderate, or severe PH, based on previously published definitions.[7] For 19 patients (73%), echocardiography and catheterization indicated placement in the same cohort. In 6 cases (23%), PH severity by catheterization was greater than predicted by echocardiogram, and PH was

**Table. Demographic and catheterization data**

| Variable | Entire cohort (n = 26) | Nonreactive (n = 17) | Reactive (n = 9) | *P* value |
|---|---|---|---|---|
| Birth weight (kg) | 0.58 (0.5-0.74) | 0.54 (0.47-0.69) | 0.69 (0.61-1.86) | **.0032** |
| Gestational age at birth (wk) | 26 (24-29) | 26 (24-27) | 28 (26-31) | **.0323** |
| Age at catheterization (d) | 156 (112-180) | 164 (125-237) | 151 (73-180) | .1566 |
| Corrected age at catheterization (wk) | 47 (44-56) | 47 (45-55) | 46 (44-52) | .4453 |
| Weight at catheterization (kg) | 4.1 (2.7-5.5) | 3.9 (2.7-5.7) | 4.9 (3.1-5.5) | .8026 |
| Invasive ventilation at catheterization | 10 (38) | 7 (41) | 3 (33) | .6957 |
| Any PH therapy at catheterization | 12 (46) | 9 (53) | 3 (33) | .3400 |
| Any Diuretic at catheterization | 20 (77) | 15 (88) | 5 (55) | .0599 |
| mPAP (mm Hg) | 29 (24-35) | 28 (23-31) | 30 (29-46) | .0572 |
| sPAP (mm Hg) | 50 (41-57) | 47 (40-56) | 53 (50-69) | .1538 |
| PVRi (WU*$m^2$) | 5.3 (3.5-6.9) | 4 (2.4-6.7) | 6.7 (5.2-8.2) | **.0059** |
| PAWP (mm Hg) | 8 (7-10) | 8 (7-10) | 7 (6-10) | .2866 |
| PAWP > 10 mm Hg | 6 (23) | 4 (24) | 2 (22) | .9400 |
| PASP% (%) | 68 (58-85) | 62 (55-82) | 81 (67-93) | .0653 |
| Pulmonary vein stenosis | 7 (27) | 6 (35) | 1 (11) | .1860 |
| Total duration on ventilator (d) | 113 (21-320) | 142 (63-291) | 70 (16-320) | .3601 |
| Hospitalization (d) | 247 (173-363) | 272 (175-375) | 223 (162-307) | .3172 |
| Tracheostomy | 5 (19) | 5 (29) | 0 (0) | - |
| Death | 6 (23) | 5 (29) | 1 (11) | .2108 |
| Tracheostomy or death | 10 (38) | 9 (53) | 1 (11) | **.0370** |

*mPAP*, mean pulmonary artery pressure; *sPAP*, systolic PA pressure; *PAWP*, PA wedge pressure; *PASP%*, PA systolic pressure percent of systemic systolic pressure.
All data are represented as median (IQR) or n (%). *P* values refer to comparisons between reactive and nonreactive groups. **Bold** signifies $P < .05$.

determined as less severe in 1 patient. Pulmonary vein stenosis was suspected by echocardiography in 3 of the 7 cases subsequently confirmed by cardiac catheterization.

An active change in clinical management that followed cardiac catheterization was identified in 65% of participants, including 13 participants (50%) who had a medication change (either initiated or discontinued) and 6 patients (23%) who had an intervention performed during the catheterization. Findings from the catheterization results in the remaining patients included the absence of associated cardiovascular lesions requiring intervention and led to decisions to not add further PH therapies. There was no significant association between a change in management and results of AVT ($P = .73$) or meeting the combined outcome of death or tracheostomy ($P = .35$).

Four patients (15%) had complications related to their procedure, 3 in the nonreactive group and 1 in the reactive group (19% vs 11%, $P = .62$). Three events were considered minor (2 vascular thromboses requiring anticoagulation but without need for urgent intervention and 1 episode of hemodynamically stable atrial flutter that required cardioversion). One major complication occurred, which was a ventricular tachycardia that required defibrillation. There were no catheterization-related deaths or episodes of PH crisis in the cohort.

AVT was performed for all participants (Figure 1). Nine participants (35%) had positive AVT with an average decrease in mean PA pressure from 36 mm Hg (baseline) to 26 mm Hg with acute vasodilator exposure ($P = .04$). Seventeen participants had a negative AVT as defined by a physiologically insignificant change in mean PA pressure (29 mm Hg at baseline to 26 mm Hg after treatment; $P =$ NS). There was no association between a participant receiving precatheterization nitric oxide therapy and results of AVT (24% of nonresponders on inhaled nitric oxide vs 33% of responders on inhaled nitric oxide; $P = .58$). Participants with positive AVT had a higher baseline PVRi (7.4 vs 4.6 Woods units*m$^2$; $P = .04$) and a trend toward higher baseline mean PA pressure (36 mm Hg vs 29 mm Hg; $P = .19$) than those with negative AVT. There was no difference in the measured mean PA pressure or PVRi between positive and negative AVT participants during vasodilator exposure.

The association between positive AVT and clinical variables is shown in the Table. Participants with positive AVT had a greater gestational age (28 weeks vs 26 weeks) and birth weight (690 g vs 540 g), but no difference in age or weight at catheterization. One participant in the reactive group and 9 participants in the nonreactive group met the combined outcome of tracheostomy or death, and AVT-positive participants were less likely to meet the combined outcome of death/tracheostomy (11% vs 53%; $P = .03$) than AVT-negative patients. Those with positive AVT trended toward shorter mechanical ventilation times and shorter hospitalizations, but these factors did not attain statistical significance.

Cox proportional hazards and Kaplan-Meier survival analyses were performed to further investigate the relationship between AVT and the combined outcome of death or tracheostomy (Figure 2). Negative AVT was prognostic for the combined outcome (hazard ratio, 0.15; $P = .02$; Figure 3).

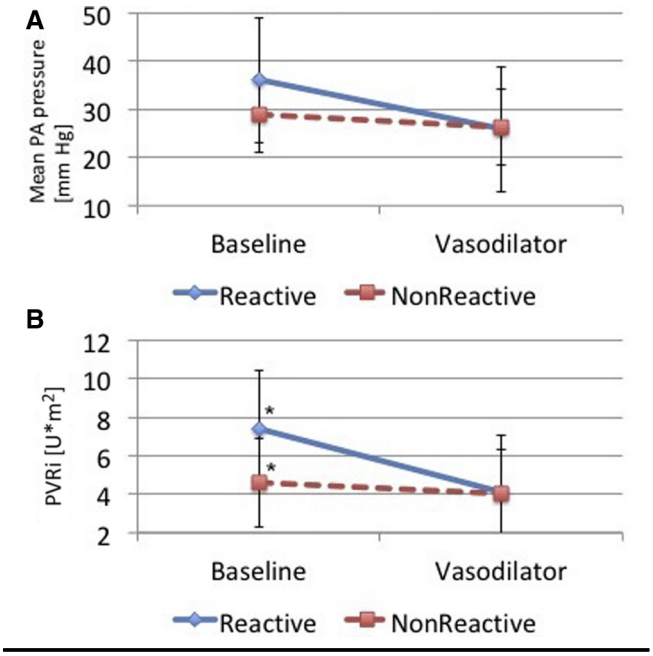


**Figure 1.** Results of AVT. **A,** Change in mean PA pressure from baseline condition to after addition of vasodilator therapy in reactive and nonreactive participants. **B,** Change in PVRi from baseline condition to after addition of vasodilator therapy in reactive and nonreactive participants. Data are presented as median ± IQR. *$P < .05$.

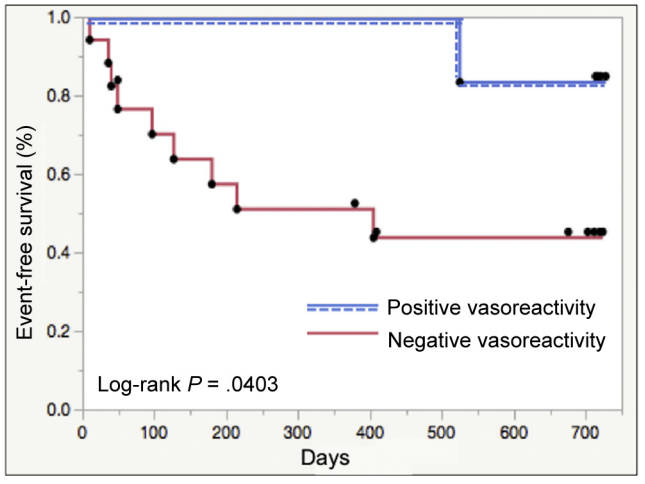


**Figure 2.** Kaplan-Meier survival curve displaying the relationship between results of AVT and freedom from the combined outcome of death or tracheostomy.

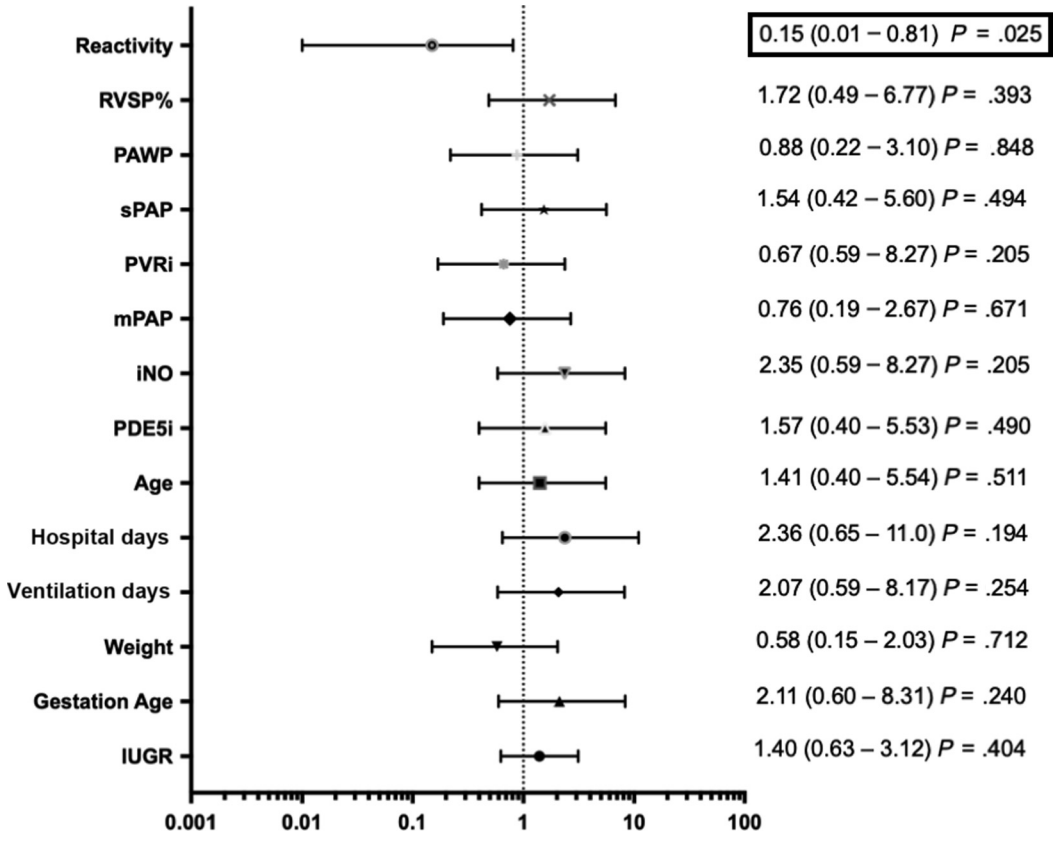


**Figure 3.** Forrest plot depicting the results of Cox proportional hazard testing. Data are presented as hazard ratio (95% CI). *INO*, inhaled nitric oxide; *IUGR*, intrauterine growth restriction; *mPAP*, mean pulmonary artery pressure; *PAWP*, PA wedge pressure; *PSE5i*, phosphodiesterase-5 inhibitors; *RVSP*, right ventricular systolic pressure; *sPAP*, systolic PA pressure.

Kaplan-Meier analysis demonstrated greater event-free survival among the AVT-positive group than the AVT-negative group ($P$ = .04). None of the baseline clinical variables or baseline catheterization parameters were prognostic for the combined outcome.

## Discussion

In this study, we found that baseline pulmonary hemodynamics were not associated with long-term outcomes, and that infants who were AVT positive as defined by the standard Barst criteria had higher mean PA pressure and PVRi at baseline than AVT negative participants.[24] AVT was positive in 35% of participants, and this subgroup had a lower risk of death or tracheostomy when compared with the AVT-negative group. We further found that 23% of our participants had elevated LV end-diastolic pressure and 27% had pulmonary vein stenosis. Overall, our study suggests that, for BPD-associated PH, AVT, but not baseline PA pressure or PVRi, may be associated with long-term outcomes, and suggests that baseline PVRi alone may be insufficient to determine a patient's risk of adverse outcome.

Previous studies have shown the value of AVT to identify lower risk individuals in other patient populations. Studies by Sitbon et al and Barst et al have proposed validated criteria to identify positive responders and an association with decreased short and long-term morbidity.[8,24,25] Among adults and children with idiopathic or familial PAH, patients with positive AVT have better long-term outcomes compared with their nonreactive counterparts.[17,26,27] Further studies have suggested a role for AVT in determining operability in patients with PAH and congenital heart disease.[28] del Cerro et al reported the cardiac catheterization of 14 infants with BPD and PH and found a similar severity of baseline disease hemodynamics as in our cohort, with a median PVRi of 4.3 units*$m^2$ and PA to systemic arterial pressure ratios of 78%.[4] However, they did not find specific perinatal factors or baseline catheterization metrics that predicted the risk of mortality and did not evaluate AVT.

We found that participants with positive AVT had higher baseline PVRi than nonreactive participants despite similar weight at catheterization, rate of mechanical ventilation, and medical therapy. These findings suggest that, in some patients, high pulmonary vascular tone and altered vasoreactivity contribute significantly to BPD-associated PH and, in other patients, structural factors, including hypertensive remodeling and decreased vascular growth, predominate. These findings also suggest that combination therapies of PH-targeted drugs, which are mostly directed toward

vasodilation, may be warranted in the management of PH. Future studies are needed to further investigate these findings in larger cohorts.

Cardiac catheterization was important in the care of our cohort to determine the physiology, evaluate for comorbidities, and guide clinical care. The findings during cardiac catheterization led to a change in management in 65% of our cases. We identified some instances in which cardiac catheterization confirmed data previously suggested by clinical examination and echocardiography. However, in others, cardiac catheterization provided new information on PH severity, LV diastolic dysfunction, or PVS that was insufficiently assessed by echocardiography alone. Importantly, 4 of the 7 infants with PVS were not diagnosed before catheterization. Although not statistically significant, 6 infants in the nonreactive group were diagnosed with PVS vs 1 participant in the reactive group.

Although these investigations have potential benefits, patient selection must be considered carefully. Catheterization in premature infants has been shown in multiple studies to be a high-risk procedure.[12,15,16] In our cohort, complications occurred in 4 participants (15%), with 1 infant having a major complication (ventricular tachycardia requiring defibrillation).

Recent guidelines recommend that cardiac catheterization be considered to evaluate the potential contribution of LV diastolic dysfunction, PVS, and shunt lesions in patients with BPD and severe PH by echocardiography, and for those infants whose PH fails to improve despite optimization of respiratory status.[5] However, these guidelines do not address AVT or a role for catheterization to add prognostic information. Our results suggest that the assessment of AVT may provide useful information regarding the severity of pulmonary vascular disease and BPD, but further studies are needed to determine whether the AVT response is useful for determining specific PH-targeted drugs or the earlier application of more aggressive clinical strategies.

The pathophysiology of PH in infants with BPD is multifactorial, with lung, cardiac, and vascular components. Disruption in vascular and alveolar growth owing to preterm birth and lung injury can decrease the cross-sectional area of the pulmonary capillaries, and decreased endothelial function may further limit airspace growth in the developing lung owing to the disruption of angiocrine signaling.[22] In addition, pulmonary vasoconstriction, especially in the setting of intermittent or chronic hypoxemia, can cause further increases in the PVRi.[9] Increased vascular tone and abnormal vasoreactivity provides a target for PH-specific vasodilator therapy. Vascular disease can also reflect degree of hypertensive remodeling or decreased vascular growth. Our data do not directly link AVT with a specific mechanism or clinical risk factor, because the failure to respond acutely to oxygen and inhaled nitric oxide may represent abnormal vasodilator mechanisms, arterial remodeling, or decreased lung vascular growth. Further studies are needed to determine whether AVT changes with time, especially in infants with BPD who show progressive clinical improvement. However, repeat assessments are difficult to perform owing to concerns about the invasive nature of the catheterization studies unless there are strong clinical indications. The assessment of AVT by relatively noninvasive means such as echocardiogram and MRI may provide novel strategies for such assessments in the future.

This study has several limitations. Because this was a single-center study with a relatively small cohort, our ability to perform a multivariable analysis to fully evaluate the influence of potential confounders, such as gestational age, comorbidities, and perinatal factors, on results of AVT is limited. Furthermore, our study does not include the larger cohort of infants with BPD and PH at our institution who were not selected for catheterization. Further studies are needed to determine optimal timing and indications for catheterization in the BPD population, and whether the use of cardiac catheterization improves outcomes. This latter point is important, because balancing the risks and benefits of catheterization in infants with BPD remains an important part of the multidisciplinary management of these fragile patients.[15,16]

We conclude that, in infants with BPD and PH, positive AVT during cardiac catheterization is associated with a decreased risk of death or tracheostomy. Further studies are needed to confirm this observation and to determine the potential value of AVT in assessing disease risk, outcomes, and better defining clinical care strategies. The decision to proceed with catheterization remains a highly individualized one, with the need to weigh the potential diagnostic, prognostic, and therapeutic benefits against the risk of complications. ■

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## References

1. Khemani E, McElhinney DB, Rhein L, Andrade O, Lacro RV, Thomas KC, et al. Pulmonary artery hypertension in formerly premature infants with bronchopulmonary dysplasia: clinical features and outcomes in the surfactant era. Pediatrics 2007;120:1260-9.
2. An HS, Bae EJ, Kim GB, Kwon BS, Baek JS, Kim EK, et al. Pulmonary hypertension in premature infants with bronchopulmonary dysplasia. Korean Circ J 2010;40:131-6.
3. Slaughter JL, Pakrashi T, Jones DE, South AP, Shah TA. Echocardiographic detection of pulmonary hypertension in extremely low birth weight infants with bronchopulmonary dysplasia requiring prolonged positive pressure ventilation. J Perinatol 2011;31:635-40.
4. del Cerro MJ, Sabate Rotes A, Carton A, Deiros L, Bret M, Cordeiro M, et al. Pulmonary hypertension in bronchopulmonary dysplasia: clinical findings, cardiovascular anomalies and outcomes. Pediatr Pulmonol 2014;49:49-59.
5. Krishnan U, Feinstein JA, Adatia I, Austin ED, Mullen MP, Hopper RK, et al. Evaluation and management of pulmonary hypertension in children with bronchopulmonary dysplasia. J Pediatr 2017;188:24-34.e1.
6. Abman SH, Hansmann G, Archer SL, Ivy DD, Adatia I, Chung WK, et al. Pediatric Pulmonary hypertension: guidelines from the American Heart Association and American Thoracic Society. Circulation 2015;132:2037-99.
7. Mourani PM, Sontag MK, Younoszai A, Ivy DD, Abman SH. Clinical utility of echocardiography for the diagnosis and management of pulmonary vascular disease in young children with chronic lung disease. Pediatrics 2008;121:317-25.

8. Douwes JM, Humpl T, Bonnet D, Beghetti M, Ivy DD, Berger RM, et al. Acute vasodilator response in pediatric pulmonary arterial hypertension: current clinical practice from the TOPP Registry. J Am Coll Cardiol 2016;67:1312-23.
9. Abman SH, Wolfe RR, Accurso FJ, Koops BL, Bowman CM, Wiggins JW. Pulmonary vascular response to oxygen in infants with severe bronchopulmonary dysplasia. Pediatrics 1985;75:80-4.
10. Berman W, Yabek S, Dillon T, Burstein R, Corlew S. Evaluation of infants with bronchopulmonary dysplasia using cardiac catheterization. J Pediatr 1982;70:708-12.
11. Del Cerro MJ, Moledina S, Haworth SG, Ivy D, Al Dabbagh M, Banjar H, et al. Cardiac catheterization in children with pulmonary hypertensive vascular disease: consensus statement from the Pulmonary Vascular Research Institute, Pediatric and Congenital Heart Disease Task Forces. Pulm Circ 2016;6:118-25.
12. Bergersen L, Gauvreau K, Marshall A, Kreutzer J, Beekman R, Hirsch R, et al. Procedure-type risk categories for pediatric and congenital cardiac catheterization. Circ Cardiovasc Interv 2011;4:188-94.
13. Twite MD, Friesen RH. The anesthetic management of children with pulmonary hypertension in the cardiac catheterization laboratory. Anesthesiol Clin 2014;32:157-73.
14. O'Byrne ML, Glatz AC, Hanna BD, Shinohara RT, Gillespie MJ, Dori Y, et al. Predictors of catastrophic adverse outcomes in children with pulmonary hypertension undergoing cardiac catheterization: a multi-institutional analysis from the Pediatric Health Information Systems Database. J Am Coll Cardiol 2015;66:1261-9.
15. O'Byrne ML, Kennedy KF, Kanter JP, Berger JT, Glatz AC. Risk factors for major early adverse events related to cardiac catheterization in children and young adults with pulmonary hypertension: an analysis of data from the IMPACT (Improving Adult and Congenital Treatment) Registry. J Am Heart Assoc 2018;7.
16. Jassal A, Cavus O, Bradley EA. Pediatric and adolescent pulmonary hypertension: what is the risk of undergoing invasive hemodynamic testing? J Am Heart Assoc 2018;7.
17. Sharma A, Obiagwu C, Mezue K, Garg A, Mukherjee D, Haythe J, et al. Role of vasodilator testing in pulmonary hypertension. Prog Cardiovasc Dis 2016;58:425-33.
18. Ploegstra MJ, Zijlstra WM, Douwes JM, Hillege HL, Berger RM. Prognostic factors in pediatric pulmonary arterial hypertension: a systematic review and meta-analysis. Int J Cardiol 2015;184:198-207.
19. Barst RJ, Ivy DD, Foreman AJ, McGoon MD, Rosenzweig EB. Four- and seven-year outcomes of patients with congenital heart disease-associated pulmonary arterial hypertension (from the REVEAL Registry). Am J Cardiol 2014;113:147-55.
20. Rich S, Martinez J, Lam W, Levy PS, Rosen KM. Reassessment of the effects of vasodilator drugs in primary pulmonary hypertension: guidelines for determining a pulmonary vasodilator response. Am Heart J 1983;105:119-27.
21. Frank BS, Ivy DD. Diagnosis, Evaluation and treatment of pulmonary arterial hypertension in children. Children (Basel) 2018;5.
22. Abman SH, Baker C, Gien J, Mourani P, Galambos C. The Robyn Barst Memorial Lecture: differences between the fetal, newborn, and adult pulmonary circulations: relevance for age-specific therapies (2013 Grover Conference series). Pulm Circ 2014;4:424-40.
23. Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2013;62:D34-41.
24. Barst RJ. Pharmacologically induced pulmonary vasodilatation in children and young adults with primary pulmonary hypertension. Chest 1986;89:497-503.
25. 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.
26. Leuchte HH, Baezner C, Baumgartner RA, Muehling O, Neurohr C, Behr J. Residual pulmonary vasodilative reserve predicts outcome in idiopathic pulmonary hypertension. Heart 2015;101:972-6.
27. Barst RJ, Agnoletti G, Fraisse A, Baldassarre J, Wessel DL , NO Diagnostic Study Group. Vasodilator testing with nitric oxide and/or oxygen in pediatric pulmonary hypertension. Pediatr Cardiol 2010;31:598-606.
28. Viswanathan S, Kumar RK. Assessment of operability of congenital cardiac shunts with increased pulmonary vascular resistance. Catheter Cardiovasc Interv 2008;71:665-70.