Reliability of Echocardiographic Indicators of Pulmonary Vascular Disease in Preterm Infants at Risk for Bronchopulmonary Dysplasia

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Objectives To determine the assessment and inter-rater reliability of echocardiographic evaluations of pulmonary vascular disease (PVD) in preterm infants at risk for bronchopulmonary dysplasia.

Study design We prospectively studied echocardiograms from preterm infants (birthweights 500-1250 g) at 7 days of age and 36 weeks postmenstrual age (PMA). Echocardiograms were assessed by both a cardiologist on clinical service and a single research cardiologist. Interpretations were reviewed for inclusion of determinants of PVD and assessed for inter-rater reliability using the Prevalence Adjusted Bias Adjusted Kappa Score (PABAK).

Results One hundred eighty and 188 matching research and clinical echocardiogram reports were available for the 7-day and 36-week PMA studies. At least one of the specific qualitative measures of PVD was missing from 54% of the clinical reports. PVD was diagnosed at 7 days in 31% and 20% of research and clinical interpretations, respectively (PABAK score of 0.54). At 36 weeks, PH was diagnosed in 15.6% and 17.8% of research and clinical interpretations, respectively (PABAK score of 0.80).

Conclusions Although all qualitative variables of PVD are not consistently provided in echocardiogram reports, the inter-rater reliability of cardiologists evaluating measures of PVD revealed strong agreement, especially at 36 weeks PMA. We speculate that establishment of a protocol for echocardiographic evaluation may improve the identification of PVD in preterm infants. *(J Pediatr 2017;186:29-33).*

Preterm infants are at high risk for late respiratory morbidity and mortality due to the development of bronchopulmonary dysplasia (BPD), the chronic lung disease of preterm infants.[1-3] Animal models reveal that early disruption of angiogenesis impairs alveolarization and causes sustained abnormalities of lung function, suggesting that pulmonary vascular disease (PVD) may contribute to the pathogenesis of BPD.[4] Pulmonary hypertension (PH) is a clinical manifestation of PVD that is a significant complication in preterm infants who develop BPD and is associated with significant morbidity and mortality, as evidenced by a 2-year mortality rate of 33%-48% after PH diagnosis.[5,6] Recent data suggest the incidence of PH in extremely preterm infants is 17%-34%, indicating that routine screening may be useful for identifying infants at increased risk.[5,7-11] Moreover, signs of early PVD have been associated with increased risk for BPD and late PH.[12] Despite its impact on the clinical course of BPD, making the diagnosis of early PVD or PH is difficult because signs and symptoms are often subtle and similar to those of lung disease alone. The early identification of PVD or PH in preterm infants may provide an opportunity for implementation of preventative or treatment strategies to improve long-term outcomes.

Although cardiac catheterization remains the gold standard for the diagnosis of PH, transthoracic echocardiography offers noninvasive, readily available testing.[13] A commonly used objective echocardiographic measure of PH is the estimated right ventricular systolic pressure (RVSP), which is derived from the tricuspid regurgitant jet velocity (TRJV) and modified Bernoulli equation ($TRJV^2 \times 4$).[14] The pattern of shunting through a ventricular septal defect (VSD) or patent ductus arteriosus (PDA) also provides a semiquantitative assessment of the resistance between the pulmonary and systemic vascular beds. Qualitative findings include septal wall flattening, right ventricular (RV) hypertrophy (RVH), right atrial dilation, and RV dilation, but these are not as reliable for determining PH severity, especially in the absence of a measurable TRJV.[7] In a prior prospective study, RVSP could be estimated from TRJV in only 8% of preterm infants.[12] Therefore, evaluation of PVD in this population routinely requires the application of qualitative echocardiographic measures.

BPD	Bronchopulmonary dysplasia	RV	Right ventricular
PABAK	Prevalence Adjusted Bias Adjusted Kappa Score	RVH	RV hypertrophy
		RVSP	Right ventricular systolic pressure
PDA	Patent ductus arteriosus	TRJV	Tricuspid regurgitant jet velocity
PMA	Postmenstrual age	VSD	Ventricular septal defect
PVD	Pulmonary vascular disease	3D	3-dimensional
REDCap	Research Electronic Data Capture		

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The physiological decrease in pulmonary vascular resistance after birth also complicates assessment for PVD. The optimal timing for this transition and the clinical impact of "delayed" or "incomplete" transition is not well understood. Findings of increased pulmonary vascular resistance, right ventricular hypertrophy, or right atrial dilation, may be physiologically normal and not evidence for PVD or PH. Moreover, qualitative measures of PVD may not be routinely included in the clinical echocardiogram report during the early postnatal period. In addition, echocardiograms are often performed to evaluate for anatomic abnormalities and cardiac function, which may not direct the interpreting cardiologist to comment on each sign of PVD.

We hypothesized that subjective variables of PVD are not consistently communicated in clinical echocardiogram reports, but when reported, show good agreement between their interpretations in preterm infants at early (day 7) and late (36 weeks postmenstrual age [PMA]) time points. As part of a prospective observational study to determine the incidence and risk factors for BPD in preterm infants,[12] we evaluated the consistency of interpretation of measures of PVD in echocardiograms performed at 7 days of age and 36 weeks PMA between a research cardiologist blinded to clinical course and the clinical echocardiography service.

Methods

All echocardiograms and data were prospectively obtained as part of an observational research study that enrolled subjects between July 2006 and March 2012 at 3 hospitals associated with The University of Colorado School of Medicine and 5 hospitals affiliated with Indiana University School of Medicine.[12] The protocol was approved by the Institutional Review Boards at each site, and written informed consent was obtained from a parent or guardian of all participants.

Enrollment criteria consisted of birth weight 500-1250 g, gestational age less than 34 weeks PMA, and enrollment by 7 days of age. Exclusion criteria included clinical evidence of congenital heart disease (except PDA, atrial septal defect less than 1 cm or VSD less than 2 mm), lethal congenital abnormality, and/or anticipated death.

Echocardiograms were performed at 7 days of age and at 36 weeks PMA using a standardized image acquisition protocol for each patient. All sonographers were trained on the protocol by the lead sonographer via teleconference with a PowerPoint presentation. As studies were reviewed centrally, feedback was provided to individual sonographers to improve image quality. Research interpretation for all echocardiograms was performed by a single cardiologist at Children's Hospital Colorado blinded to the subjects' clinical status. Measurements included TRJV, measurable dimensions of heart chambers, any detectable shunt lesions (patent foramen ovale, atrial septal defect, VSD, PDA), and direction of shunt flow. Estimates of RVSP were calculated using the modified Bernoulli equation with no allowance for right atrial pressure. If the spectral Doppler pattern of the tricuspid regurgitant jet did not provide a clearly defined and reproducible ascending limb, apex, and descending limb, assessments of TRJV were not considered as suitable for determining RVSP for these studies.

Qualitative echocardiogram measures of PVD and increased right ventricular pressure were evaluated including right atrial enlargement, right ventricular dilation, RVH, ventricular septal wall flattening, and pulmonary artery dilation. Abnormalities in these measures were assessed by degree of severity: mild, moderate, or severe. Septal wall flattening was defined as decreased septal curvature into the right ventricle at end systole. Septal wall flattening was considered moderate if the septum was completely flat ("D shaped") and severe if there was reverse curvature into the left ventricle.

The echocardiograms were first interpreted in real-time by one of 18 local clinical cardiologists to provide results in a timely fashion to caregivers. Clinical echocardiogram reports were obtained retrospectively by review of medical records. We did not have access to the medical records from some of the affiliated hospitals to collect all of the clinical echocardiogram reports. The presence of any of the following variables was sufficient for the diagnosis of PH in our analyses at 36 weeks PMA: any degree of right ventricle hypertrophy, right ventricle dilation, or septal wall flattening. In the absence of specific documentation of subjective PH variables, the following statements were accepted as negative findings: "normal right heart chamber size and right systolic function" and "no 2-dimensional evidence of right ventricle pressure or volume overload."

Statistical Analyses

All data were managed in a Research Electronic Data Capture (REDCap) database hosted at the University of Colorado Denver Development and Informatics Service Center.[15] The prevalence adjusted bias adjusted kappa (PABAK) score was used to assess agreement between cardiologists' evaluation of echocardiogram evidence of PVD or PH.[16] This measure accounts for the bias that occurs with the high or low prevalence of a given response and was calculated on each echocardiogram indicator. PABAK scores were interpreted using established methods[16] and were interpreted as the following: <0 less than chance agreement; .01-0.20 slight agreement; 0.21-0.40 fair agreement; 0.41-0.60 moderate agreement; 0.61-0.80 substantial agreement; and 0.81-0.99 almost perfect agreement.[17]

Results

Three hundred sixteen infants were enrolled in the parent study between July 2006 and March 2012. Of the enrollees, 277 survived and had an echocardiogram performed at 36 weeks PMA.[12] Clinical echocardiogram reports were not available for 66 infants who had research echocardiograms performed, leaving 211 infants with at least 1 set of matching research and clinical echocardiogram interpretations available for analysis. These included 188 paired interpretations for the 7-day echocardiograms and 180 paired interpretations for the 36-week echocardiograms. The discrepancy between infants enrolled and the available matching echocardiogram reports was due to an inability to access all clinical reports from affiliated institutes. Clinical characteristics of study patients are shown in **Table I**.