Persistence of Pulmonary Hypertension by Echocardiography Predicts Short-Term Outcomes in Congenital Diaphragmatic Hernia

Leslie A. Lusk, MD[1], Katherine C. Wai, BS[2], Anita J. Moon-Grady, MD[3,4], Martina A. Steurer, MD[1], and Roberta L. Keller, MD[4]

Objectives To describe the natural history of pulmonary hypertension (PH) and the risk of death and pulmonary morbidity associated with the persistence of PH through the neonatal hospitalization for these infants.

Study design We performed a retrospective cohort study of infants with congenital diaphragmatic hernia (CDH) cared for at University of California San Francisco (2002-2012). Infants with other major anomalies or syndromes were excluded (n = 43). Clinical echocardiograms were performed weekly for up to 6 weeks or until PH resolved off respiratory support or until hospital discharge. Echocardiograms were re-read by a blinded reviewer and categorized by severity of elevation in estimated pulmonary arterial pressure. PH was defined as ≥2/3 systemic blood pressure. Severity was determined by a hierarchy of ductus arteriosus level shunt, interventricular septal position, and tricuspid regurgitant jet velocity.

Results Of 140 infants with ≥1 echo, 98 resolved their PH prior to death/discharge. Mean time to resolution was 18 days (median 14 days, IQR 8, 21 days). Those with persistence of PH had a higher rate of extracorporeal membrane oxygenation ($P < .001$) and death ($P < .001$), and fewer ventilator-free days ($P < .001$). Persistence of PH at 14 days predicted mortality (area under the receiver operating characteristic curve 0.87) and adverse respiratory outcomes (area under the receiver operating characteristic curve 0.80-0.83).

Conclusions The majority of infants with CDH resolve PH between 1 and 3 weeks of life. At 2 weeks of age, severity of PH by echocardiogram strongly predicts short-term pulmonary morbidity and death. Further evaluation of physiological alterations during that time may lead to novel therapies for severe CDH. *(J Pediatr 2015;166:251-6)*.

Congenital diaphragmatic hernia (CDH) is one of the most common major congenital anomalies, occurring in 1 in 4000-5000 live births.[1,2] CDH is associated with significant morbidity and mortality, primarily because of lung hypoplasia and pulmonary hypertension (PH).[3-7] However, little is known about the natural history of PH in this population. Previous studies that have attempted to characterize PH in infants with CDH have limited utility because of the inclusion of data that were collected during an earlier period of management strategies or used echocardiograms associated with clinical events, potentially biasing the results.[5,8,9] We previously demonstrated, with a limited sample size, that PH at 2 weeks was predictive of short-term clinical outcomes, with infants discharged on room air resolving their PH to a greater extent than those with persistence of PH.[10] In contrast, healthy term neonates have a rapid fall in pulmonary vascular resistance (PVR) by 72 hours of life.[11]

Although echocardiography for the assessment of PH and prediction of outcomes in infants with CDH has previously been studied,[4,5,9,10] a longitudinal evaluation of standard clinical echocardiography in a large, contemporary cohort has not been reported. Our aim was to evaluate the natural history of PH in infants with CDH, based on routine echocardiography over the first 6 weeks of life. We also evaluated PH on routine echocardiography at various time points as a biomarker for predicting the risk of death and short-term pulmonary morbidity among infants with CDH. Finally, we determined the time point that was the best predictor of a poor outcome.

Methods

This retrospective cohort study of infants cared for at the University of California San Francisco Benioff Children's Hospital (2002-2012) included patients with ≥1 echocardiogram and a posterolateral Bochdalek-type CDH. Patients with multiple congenital anomalies or confirmed or suspected syndromes were excluded. During this period, all infants with CDH had routine weekly

AUROC	Area under the receiver operating characteristic
CDH	Congenital diaphragmatic hernia
ECMO	Extracorporeal membrane oxygenation
iNO	Inhaled nitric oxide
PAp	Pulmonary arterial pressure
PH	Pulmonary hypertension
PVR	Pulmonary vascular resistance
TR	Tricuspid regurgitant

From the [1]Division of Neonatology, Department of Pediatrics, [2]School of Medicine, [3]Division of Cardiology, Department of Pediatrics, and [4]Fetal Treatment Center, University of California San Francisco, San Francisco, CA

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echocardiograms per clinical protocol. Demographic and clinical data were collected by chart review. For this study, echocardiograms were re-reviewed by a reader blinded to clinical outcomes of the infants. Outcomes of interest were death prior to discharge, prolonged intubation (≥28 days), and chronic lung disease (any respiratory support at ≥56 days of life or discharge on oxygen prior to 56 days, based on the National Institute of Child, Health, and Human Development proposed definition of moderate-to-severe bronchopulmonary dysplasia for infants ≥32 weeks gestational age).[12] The University of California San Francisco Institutional Review Board approved this study.

Beginning in 2002, infants with CDH had routine echocardiograms (Acuson Sequoia C256, C512, and SC2000; Siemens, Mountain View, California) within the first 48 hours of life, then weekly for the first 6 weeks or until death, discharge, or resolution of PH off respiratory support. Infants did not routinely receive additional sedation for echocardiography. Blood pressure, heart rate, and weight at the time of the scan were recorded. Standard clinical echocardiographic views were used to estimate pulmonary arterial pressure (PAp) compared with systemic systolic blood pressure at the time of the scan, to categorize degree of PH. Infants were classified as follows: <2/3 systemic systolic pressures (no/mild PH), ≥2/3 systemic-to-systemic pressure (moderate PH), or systemic-to-suprasystemic pressure (severe PH), as previously described.[10] Classification was by a hierarchy of assessments: (1) direction and velocity of ductus arteriosus flow using the Bernoulli equation; (2) interventricular septum position (parasternal short axis), graded as normal, flattened, or D-shaped; and (3) right ventricular pressures using peak tricuspid regurgitant (TR) jet velocity estimated by the modified Bernoulli equation (assuming a right atrial pressure of 0 mm Hg).

All patients were intubated immediately after birth and managed with a gentle ventilation strategy of pressure limitation and permissive hypercapnia. High frequency oscillatory ventilation was used for patients with refractory hypercapnia or high peak inspiratory pressures. Inhaled nitric oxide (iNO) was initiated at 20 ppm for poor oxygenation secondary to PH. Patients received extracorporeal membrane oxygenation (ECMO) support if they continued to have refractory hypoxemia or evidence of inadequate oxygen delivery despite optimal support. Surgical repair followed clinical stabilization. Clinical practice evolved over the study years, with increasing use of assisted ventilation (earlier extubation to nasal continuous positive airway pressure) and a decrease in duration of ECMO support, following an internal review demonstrating poor survival to discharge among infants with CDH on ECMO support for ≥10 days.

Statistical Analyses

Data were analyzed by χ^2 and rank sum or t tests as appropriate. Time to resolution of PH (<2/3 systemic pressure) was assessed by Kaplan-Meier survival curves. Sensitivity, specificity, positive predictive value, and negative predictive value were calculated to assess the utility of PH severity classification by echocardiogram at 1, 2, 3, 4, and 6 weeks. Area under the receiver operating characteristic (AUROC) curves were used to determine the overall predictive accuracy at these time points (Stata 12.0; StataCorp, College Station, Texas).

Results

One hundred forty infants met inclusion criteria (including 39 infants previously reported in our prospective study[10]); 43 were excluded because of multiple anomalies, a genetic syndrome, or Morgagni hernia, and 5 infants were excluded for having no available echocardiogram (**Figure 1**; available at www.jpeds.com). Of those included, most infants were term (mean gestational age 38 ± 2.4 weeks) with a predominance of male infants and left-sided defects. There was a range of severity; lung-to-head ratio was <1 in 36% of fetuses with measurements and liver was herniated into the thorax in 58% of 133 newborns. Prostaglandin E1 was used to maintain ductal patency in the setting of severe suprasystemic PH in only 10% of infants, though this practice was not routinely considered for use until 2008 (**Table I**).

PH was classified for 597 echocardiograms. Of these, only 38% of scans had a quantifiable TR jet. Studies demonstrating severe PH were significantly more likely to have a measurable TR envelope than those with mild/no PH (81% vs 19%, $P < .001$). The ductus arteriosus was open with measurable direction/velocity in 58% of scans, specifically, 85% in the first 48 hours of life and 43%, 26%, 23%, and 19% at 1, 2, 3, and 4 weeks of life, respectively. Septal position was interpretable in 97% of scans. All 3 variables were evaluable in only 20% of echocardiograms. Week 1 echos were performed at a median of 8 days of life (IQR 7-9 days), week 2 at a median of 15 days (IQR 14-17 days), week 3 at a median of 22 days (IQR 21-28 days), week 4 at a median of 29.5 days (IQR 28-37 days), and week 6 at a median of 49 days (IQR 42-64 days).

Of the 140 patients, 42 (30%) never resolved their PH prior to death or discharge. Among those who did resolve, the mean time to resolution was 17 days (median 14 days, IQR 7, 21; **Figure 2**). Although overall mortality was not high (19%), the risk of death was significantly lower among infants who resolved their PH compared with those who did not (1% vs 60%, $P < .001$). Only 2 infants died after their PH resolved. One was a preterm infant with necrotizing enterocolitis. The other was a term infant who died of respiratory failure after resolution of PH. Patients who resolved their PH had decreased rates of iNO and prostaglandin E1 use, need for ECMO support and nonprimary repair, and an increase in ventilator-free days by 28 days of age (**Table I**). Right-sided defects were more common among those with no resolution of PH, although this did not reach statistical significance.

Among the 8 infants who resolved their PH within the first week of life, there were no subsequent adverse outcomes including death, prolonged intubation, or prolonged