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Prenatal pulmonary hypertension index: novel prenatal predictor of severe postnatal pulmonary artery hypertension in antenatally diagnosed congenital diaphragmatic hernia

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Abstract

Purpose—This study aim to assess the potential of prenatal predictors of postnatal severe pulmonary artery hypertension (PAH) in isolated left congenital diaphragmatic hernia (CDH) and to define a new prenatal pulmonary hypertension index (PPHI).

Methods—A retrospective chart review of CDH patients between May 2005 and October 2008 was conducted. Ten patients with systemic/suprasystemic and 9 patients with subsystemic pulmonary hypertension at 3 weeks of age were identified. Diameters of the right pulmonary artery, left pulmonary artery (LPA_d), aorta, and the length of vermis of the cerebellum were obtained from prenatal magnetic resonance imaging to calculate the PPHI $[(LPA_d / \text{length of vermis of the cerebellum}) \times 10]$ and the modified McGoon index (MGI) $[(\text{diameter of the right pulmonary artery} + LPA_d) / \text{diameter of aorta}]$. Prenatal pulmonary hypertension index and MGI were compared with lung-to-head ratio, percent predicted lung volume, and total lung volume for pulmonary hypertension and survival.

Results—The PPHI and MGI had a significant, negative correlation with pulmonary hypertension ($r = -0.61$, $P = .005$, and $r = -0.72$, $P < .005$, respectively). The PPHI and MGI are significantly lower in the systemic/suprasystemic PAH group compared with the subsystemic PAH group (1.11 ± 0.32 versus 1.63 ± 0.28 , $P = .004$, and 0.71 ± 0.15 versus 1.05 ± 0.11 , $P < .001$, respectively). There were no significant differences between the groups comparing the lung-to-head ratio, percent predicted lung volume, and total lung volume.

Conclusion—Both PPHI and MGI accurately predict the severity of postnatal PAH in isolated left CDH.

Keywords

Congenital diaphragmatic hernia; Pulmonary hypertension; McGoon index; Prenatal diagnosis

Recent advances in managing cardiorespiratory support for congenital diaphragmatic hernia (CDH) have likely contributed to the improved survival rates [1,2]. In patients with CDH, abnormal persistence of elevated pulmonary vascular resistance in the form of pulmonary artery hypertension (PAH) is recognized as an important component of the pathophysiology of the disease. The evolution of pulmonary hypertension has been reported to be a critical determinant of mortality and morbidity in CDH patients [3]. As a result of advances in prenatal imaging, biometric parameters used for risk stratification have been developed and survival rates are better predicted [4,5]. However, prenatal prognostic factors such as lung-to-head ratio (LHR), percent predicted lung volume (PPLV), and total lung volume (TLV) rely entirely on lung size or volume to predict the degree of pulmonary hypoplasia and do not seem to correlate with the severity of pulmonary hypertension postnatally. Based on other recent prenatal and postnatal echocardiographic studies that reported pulmonary vascular measurements as predictors of outcome in CDH [6-8], in this pilot study, we evaluated 2 potential prenatal predictors of pulmonary hypertension, the modified McGoon index (MGI) and prenatal pulmonary hypertension index (PPHI) in isolated left CDH and compared them with LHR, PPLV, and TLV using the novel methodology of extreme discordant phenotype.

1. Methods

1.1. Patient data

A retrospective review of the medical records of 42 infants with CDH treated postnatally at Cincinnati Children's Hospital Medical Center between May 2005 and October 2008 was performed. This study is approved by the institutional review board (IRB# 2008- 0316). Patients with isolated left CDH and had both prenatal ultrasonography and fetal ultrafast magnetic resonance imaging (MRI) at the Fetal Care Center of Cincinnati were selected for the study. Data collected included gestation age at prenatal imaging studies, gestation age at birth, results of prenatal imaging studies and postnatal echocardiographic examinations, and outcome.

1.2. Extreme discordant phenotype model

To determine if the MGI or PPHI could discriminate severe from mild pulmonary hypertension in left-sided CDH, we used the novel concept of extreme discordant phenotype [9]. This concept adapted from pharmacogenetics compares the effects of a drug in 2 groups of patients discordant for phenotypic response to maximize ability to distinguish different responses between 2 groups. This allows a reduction in the sample size and increases the power of the study to detect differences between the 2 groups. We defined our discordant groups as (i) systemic or suprasystemic PAH (SSPAH), those cases of severe CDH with systemic or suprasystemic pulmonary hypertension by echocardiographic assessment at 3 weeks of age, consistent with severe pulmonary hypertension ($n = 10$), and (ii) subsystemic PAH (SuPAH), those patients whose pulmonary pressure was clearly subsystemic and on the way to normalization at 3 weeks of age ($n = 9$).

1.3. Prenatal studies

The LHR was obtained from ultrasonographic cross-sectional images of the fetal thorax at the level of 4-chamber view of the heart and is defined as the product of the orthogonal diameters of the right lung divided by the head circumference, as described by Metkus et al [10].

Fetal ultrafast MRI was performed using a 1.5-T scanner (Horizon; General Electric Medical System, Milwaukee, WI) without maternal or fetal sedation. All studies were optimized using various torso-phased array coils as appropriate for maternal size.

Imaging consisted of single-shot fast-spin echo T2-weighted and gradient-echo T1-weighted sequences. The T2-weighted sequences were performed with matrix of 224×192 , a field of view of 30 or less, and a slice thickness of 3 or 4 mm. Coronal, sagittal, and axial imaging of the head, neck, chest, and abdomen of each fetus was reviewed. T1-weighted gradient-echo imaging was obtained at a field of view of 30 to 35, a matrix of 256×192 , and slice thickness of 5 mm. The PPLV and TLV were obtained by MRI and calculated as described by Barnewolt et al [4]. Briefly, all images were analyzed by a staff radiologist who determined the volume of each lung, the thorax, and the mediastinum for each patient using a 3-dimensional rendering of the region of interest. The predicted lung volume was determined by subtracting the mediastinal volume from the total thoracic volume. Percent predicted lung volume was then calculated as the sum of the volumes of the right and left lung (TLV) divided by the predicted lung volume, multiplied by 100.

In addition, the following measurements were obtained from the fetal MRI. Specifically, the diameter of the right pulmonary artery, the diameter of the left pulmonary artery (LPA_d), and the diameter of the aorta at the diaphragmatic level were obtained from the axial plane. The midline sagittal images through the brain were used to obtain the craniocaudal length of vermis of the cerebellum (CI), which was chosen to standardize for gestation age in PPHI calculation. The PPHI was calculated as the left pulmonary artery diameter divided by the length of the cerebellum, multiplied by 10 [$\text{PPHI} = (\text{LPA}_d / \text{length of vermis of the cerebellum}) \times 10$], whereas the MGI was calculated as the sum of the diameters of the right and the left pulmonary arteries divided by the diameter of the aorta at the level of the diaphragm [$\text{MGI} = (\text{diameter of the right pulmonary artery} + \text{LPA}_d) / \text{diameter of the aorta}$].

1.4. Echocardiography

Postnatal echocardiograms were performed at the request of the treating physicians. Studies were performed on General Electric Vivid 7 ultrasound machines. Pulmonary artery pressure was estimated by tricuspid valve regurgitant jet velocity [11] when technically feasible. Flow pattern and velocity in the ductus arteriosus were assessed by both pulsed and color Doppler. Systemic or suprasystemic PAH was defined by one of the following: (1) systolic right ventricular pressure estimate equal to or greater than a simultaneous systolic blood pressure, or (2) bidirectional flow in a large patent ductus arteriosus, or (3) right to left systolic shunting in the ductus arteriosus with a quantifiable pressure estimate using pulsed Doppler.

1.5. Statistical analysis

Although the concept of extreme discordant phenotype was used to help define experimental groups for comparison, it did not change the statistical analysis as outlined below.

Results are summarized as means and SDs for continuous variables and as percentages for categorical variables. Pulmonary artery pressure is reported as the ratio of pulmonary artery pressure to systolic blood pressure (percent systemic pressure). Group comparisons of

continuous variables were made using Wilcoxon rank-sum test. The relationship between pulmonary artery pressure and predictor variables was assessed using Spearman rank correlation. Fisher's Exact test was used to determine if there was an association between survival and disease group. For each outcome, univariate logistic regression analyses were performed on the following independent variables: LHR, TLV, PPLV, MGI, and PPHI. Variables with P values less than .20 were selected as candidates for the multivariate analysis. Multicollinearity was examined among the independent variables using Spearman rank correlation and the variance inflation factor. Multivariate logistic regression analyses were performed for each outcome of interest where only 1 of the correlated variables was entered into the model at a time. Model selection included stepwise, forward selection, and backward elimination.

The results of the 3 selection methods were compared to determine if the final model contained the same predictor variables for all 3 selection methods. Exact logistic regression was used when appropriate. Receiver operating characteristic curves were generated to determine cutoff values for each of the independent variables, namely, LHR, TLV, PPLV, MGI, and PPHI.

The area under the curve was corrected using bootstrap-validated estimates. All tests were 2-sided and not adjusted for multiple testing. P values less than .05 were considered statistically significant. Analyses were performed using SAS (version 9.1; Cary, NC) and SPSS (version 17.0; Chicago, IL).

2. Results

Of the 42 patients treated at Cincinnati Children's Hospital Medical Center postnatally, we identified 19 patients with requisite fetal ultrasound and fetal ultrafast MRI studies for inclusion. These 19 patients were sorted by fetal echocardiographic finding into 2 groups based on a study obtained at 3 weeks of age. Ten patients were found to have SSPAH, whereas 9 patients had clearly SuPAH.

The mean (SD) gestation age at birth was 37.1 (2.4) weeks in the SSPAH group and 38 (0.7) weeks in the SuPAH group ($P = .93$). Overall survival was 84.2% (16/19). Survival in the SuPAH group was 100% (9/9), and in the SSPAH group, it was 70% (7/10). The mean (SD) gestation age at the measurement of the LHR was 26.4 (3.89) weeks in the SSPAH group and 27.4 (4.9) weeks in the SuPAH group ($P = .65$). The mean (SD) gestation age for the MRI evaluation was 30.9 (4.9) weeks in the SSPAH group and 32.67 (1.5) weeks in the SuPAH group ($P = .74$).

The PPHI (Fig. 1) and MGI (Fig. 2) had a significant, negative correlation with pulmonary arterial pressure in patients with isolated left CDH ($r = -0.60$, $P = .008$, and $r = -0.70$, $P = .001$, respectively). Although, there was a trend toward correlation observed between the PPLV (Fig. 3) and LHR (Fig. 4) with the level of PAP (Pulmonary artery pressure), these did not reach statistical significance ($r = -0.35$, $P = .05$, and $r = -0.45$, $P = .06$, respectively). Nonsignificant correlation was found between TLV and PAP ($r = -0.0009$, $P = .99$; Fig. 5).

The PPHI (Fig. 6) and the MGI (Fig. 7) were significantly lower in subjects with SSPAH compared with those with SuPAH (1.12 ± 0.37 versus 1.76 ± 0.51 , $P = .007$, and 0.70 ± 0.16 versus 1.10 ± 0.22 , $P < .001$, respectively). However, there were no differences between the groups comparing LHR (Fig. 8), TLV (Fig. 9), and PPLV (Fig. 10). No differences were observed between the patients who survived and those who died comparing the PPHI and the MGI. The univariate and multivariate logistic regression analysis did not show a relation

between mortality and any of the prenatal parameters, perhaps because of the small sample size in this study. However, the univariate logistic regression analysis showed that MGI ($P < .0001$) and PPHI ($P = .002$) accurately predict postnatal pulmonary hypertension, whereas the multivariate analysis showed that MGI is the best predictor for pulmonary hypertension.

Receiver operating characteristic curves were also generated to determine the best cutoff value to predict the level of PAH and compare the sensitivity and specificity of each of the prenatal parameters. These results are shown in Table 1.

3. Discussion

The results of this pilot study suggest that MRI measurement of the fetal branch pulmonary arteries, expressed as either MGI or PPHI, accurately predicts postnatal pulmonary hypertension. Of all parameters, MGI was the most sensitive predictor with smaller area of overlap between populations with severe versus mild postnatal pulmonary hypertension. All of the commonly used prenatal predictors in CDH, such as LHR, PPLV, and TLV, use various measurements of lung volume as an indicator of pulmonary hypoplasia and survival. None of these prenatal prognostic indicators predict the severity of pulmonary hypertension. This point was confirmed by direct comparison of LHR, PPLV, and TLV with MGI and PPHI. Although a trend was noted with PPLV and LHR, these did not reach statistical significance.

The significant correlation between the MGI and PPHI with pulmonary hypertension is consistent with the previously reported histologic findings of the lungs of CDH fetuses in which pulmonary vascular underdevelopment and excessive muscularization of the preacinar arteries were seen [12]. These results are also consistent with previous reports that demonstrated correlation between the degree of arborization of the pulmonary vasculature on 3-dimensional power Doppler and outcome in CDH [7].

The utility of a prognostic indicator for the severity of postnatal pulmonary hypertension could be especially helpful when used in conjunction with lung volume–based predictors of pulmonary hypoplasia (LHR, TLV, PPLV) to guide counseling and management decisions. However, the results presented should be considered preliminary, and larger prospective studies are needed to confirm the utility of MGI and PPHI and determine if the combination of MGI or PPHI with LHR, or PPLV, or TLV improves the prognostic accuracy. It will also be important to examine the effect of gestation age at ascertainment on the accuracy of prediction as well as comparing different modalities, namely, MRI, echocardiography, or ultrasound, in their accuracy of measurement of the branch pulmonary arteries and the aorta. If the MGI and PPHI were confirmed to be accurate prognostic indicators for postnatal pulmonary hypertension, they could also be used to refine the criteria for selection for prenatal treatments such as fetal tracheal balloon occlusion or delivery by ex utero intrapartum treatment with placement on extracorporeal membrane oxygenation (EXIT-to-ECMO) strategy. Furthermore, patients known to be at particularly high risk for pulmonary hypertension could be more aggressively treated with vasodilator agents, such as inhaled nitric oxide, inhaled or intravenous prostacyclin (PGI₂), with a lower threshold to move on to ECMO support should the pulmonary hypertension not respond to medical management.

The study used the concept of extreme discordant phenotype in examining patients with the most severe pulmonary hypertension and those with the mildest pulmonary hypertension to detect differences in MGI and PPHI, to reduce the sample size needed and increase the power of the study to detect differences between the groups in MGI and PPHI. This pilot study compared only patients demonstrated to have subsystemic pulmonary hypertension at 3 weeks and those with systemic or suprasystemic pulmonary hypertension at 3 weeks.

Dillon et al [3] have demonstrated that CDH patients with systemic or suprasystemic pulmonary hypertension at 3 weeks of age were at risk for increased mortality. For this reason, the 2 groups in our study were selected based on echocardiographic findings at 3 weeks of age. The analysis of extreme discordant phenotype may bias the study in favor of finding differences if they exist at all. Certainly, this approach introduces potential for identifying differences at the extremes of the clinical spectrum, and the utility in the general population must then be evaluated in a prospective study to confirm the findings. It is also possible that, in selecting the 3 weeks time-point, we may have biased toward more favorable cases of CDH in the severe group, because the most severe cases of pulmonary hypertension may have expired before 3 weeks.

To conclude, MGI and PPHI were found to accurately predict severity of postnatal pulmonary hypertension. Both MGI and PPHI seem to be superior to LHR, TLV, and PPLV in predicting severity of postnatal pulmonary hypertension. These findings will need to be confirmed in prospective studies.

References

1. Chiu P, Hedrick HL. Postnatal management and long-term outcome for survivors with congenital diaphragmatic hernia. *Prenat Diagn.* 2008; 28:592–603. [PubMed: 18551724]
2. Chiu PP, Sauer C, Mihailovic A, et al. The price of success in the management of congenital diaphragmatic hernia: is improved survival accompanied by an increase in long-term morbidity? *J Pediatr Surg.* 2006; 41(5):888–92. [PubMed: 16677876]
3. Dillon PW, Cilley RE, Mauger D, et al. The relationship of pulmonary artery pressure and survival in congenital diaphragmatic hernia. *J Pediatr Surg.* 2004; 39(3):307–12. [PubMed: 15017543]
4. Barnewolt CE, Kunisaki SM, Fauza DO, et al. Percent predicted lung volumes as measured on fetal magnetic resonance imaging: a useful biometric parameter for risk stratification in congenital diaphragmatic hernia. *J Pediatr Surg.* 2007; 42(1):193–7. [PubMed: 17208564]
5. Deprest JA, Flemmer AW, Gratacos E, et al. Antenatal prediction of lung volume and in-utero treatment by fetal endoscopic tracheal occlusion in severe isolated congenital diaphragmatic hernia. *Semin Fetal Neonatal Med.* 2009; 14:8–13. [PubMed: 18845492]
6. Sokol J, Shimizu N, Bohn D, et al. Fetal pulmonary artery diameter measurements as a predictor of morbidity in antenatally diagnosed congenital diaphragmatic hernia: a prospective study. *Am J Obstet Gynecol.* 2006; 195:470–7. [PubMed: 16777047]
7. Ruano R, Aubry MC, Barthe B, et al. Predicting perinatal outcome in isolated congenital diaphragmatic hernia using fetal pulmonary artery diameters. *J Pediatr Surg.* 2008; 43:606–11. [PubMed: 18405704]
8. Casaccia G, Crescenzi F, Dotta A, et al. Birth weight and McGoon index predict mortality in newborn infants with congenital diaphragmatic hernia. *J Pediatr Surg.* 2006; 41:25–8. [discussion 25–8]. [PubMed: 16410102]
9. Nebert DW. Extreme discordant phenotype methodology: an intuitive approach to clinical pharmacogenetics. *Eur J Pharmacol.* 2000; 410(2-3):107–20. [PubMed: 11134663]
10. Metkus AP, Filly RA, Stringer MD, et al. Sonographic predictors of survival in fetal diaphragmatic hernia. *J Pediatr Surg.* 1996; 31(1):148–51. [PubMed: 8632269]
11. Lai WW, Geva T, Shirali GS, et al. Guidelines and standards for performance of a pediatric echocardiogram: a report from the Task Force of the Pediatric Council of the American Society of Echocardiography. *J Am Soc Echocardiogr.* 2006; 19(12):1413–30. [PubMed: 17138024]
12. Nobuhara KK, Wilson JM. Pathophysiology of congenital diaphragmatic hernia. *Semin Pediatr Surg.* Nov; 1996 5(4):234–42. [PubMed: 8936652]

Fig. 1.
Correlation between the PPHI and PAP at 3 weeks of age ($r = -0.60$, $P = .008$).

Fig. 2.
Correlation between the MGI and PAP at 3 weeks of age ($r = -0.70$, $P = .001$).

Fig. 3.
Correlation between the PPLV and PAP/SAP ratio at 3 weeks of age ($r = -0.35$, $P = .05$).

Fig. 4. Correlation between the LHR and PAP at 3 weeks of age ($r = -0.45$, $P = .06$).

Fig. 5.
Correlation between the TLV and PAP at 3 weeks of age ($r = -0.0009$, $P = .99$).

Fig. 6. Retrospective data showing the mean values for PPHI in the SSPAH and SuPAH groups.

Fig. 7. Retrospective data showing the mean values for MGI in the SSPAH and SuPAH groups.

Fig. 8. Retrospective data showing the mean values for LHR in the SSPAH and SuPAH groups.

Fig. 9. Retrospective data showing the mean values for TLV in the SSPAH and SuPAH groups.

Fig. 10. Retrospective data showing the mean values for PPLV in the SSPAH and SuPAH groups.

Table 1

Prediction of postnatal pulmonary arterial hypertension using the different prenatal parameters

Prenatal parameter	Cutoff value	Sensitivity (%)	Specificity (%)	PCP (%)	AUC	Corrected AUC
MGI	0.88	90	88.9	89.5	96.7	96.2
PPHI	1.54	90	55.6	73.7	86.7	86.1
PPLV	18	50	77.8	63.2	66.1	62.6
TLV	24	50	66.7	57.9	60	57.7
LHR	12	50	88.9	68.4	72.8	70.3

PCP indicates percent correctly predicted; AUC, area under the curve; Corrected AUC, corrected area under the curve.