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Pulmonary Hypertension in Patients with Congenital Diaphragmatic Hernia: Does Lung Size Matter?

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Abstract

Purpose: The relationship between pulmonary hypoplasia and pulmonary arterial hypertension (PHTN) in patients with congenital diaphragmatic hernia (CDH) remains ill-defined. We hypothesized that prenatal estimates of lung size would directly correlate with PHTN severity.

Methods: Infants with isolated CDH (born 2004–2015) at a single institution were included. Estimates of lung size included observed-to-expected LHR (o:eLHR) and %-predicted lung volumes (PPLV=observed/predicted volumes). The primary outcome was severity of PHTN (grade 0–3) on echocardiography performed between day of life 3–30.

Results: Among 62 included patients, there was 32% mortality and 65% ECMO utilization. PPLV (odds ratio [OR]=0.94 per 1 grade in PHTN severity, 95% confidence interval [CI]=0.89–0.98, $p<0.01$) and o:eLHR (OR=0.97, 95% CI=0.94–0.99, $p<0.01$) were significantly associated with PHTN grade. Among patients on ECMO, PPLV (OR=0.92, 95% CI=0.84–0.99, $p=0.03$) and o:eLHR (OR=0.95, 95% CI=0.92–0.99, $p=0.01$) were more strongly associated with PHTN grade. PPLV and o:eLHR were significantly associated with use of inhaled nitric oxide (OR=0.90, 95% CI=0.83–0.98, $P=0.01$ and OR=0.94, 95% CI=0.91–0.98, $P<0.01$, respectively) and epoprostanol (OR=0.91, 95% CI=0.84–0.99, $P=0.02$ and OR=0.93, 95% CI=0.89–0.98, $P<0.01$, respectively).

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Conclusions: Among infants with isolated CDH, PPLV and o:eLHR were significantly associated with PHTN severity, especially among patients requiring ECMO. Prenatal lung size may help predict postnatal PHTN and associated therapies.

Introduction

Despite advances in treatment, the overall morbidity and mortality of congenital diaphragmatic hernia (CDH) remain high[1–6] due to complications of pulmonary hypoplasia and pulmonary arterial hypertension (PHTN).[6–9] Bilateral lung hypoplasia (with the ipsilateral lung most severely affected) results both from the herniation of abdominal viscera into the chest limiting lung development and from the genetic factors that control development of both the diaphragm and lungs.[10–15] Associated PHTN results from physical sequelae of lung hypoplasia including decreased cross-sectional area of the pulmonary arterial tree and hypertrophy of the pulmonary artery musculature[16–19], as well as underlying alterations in genotypic expression that result in a reduced number of bronchi and alveoli, abnormal pulmonary vasculature, and altered tracheobronchial innervation.[6,20,21]

Based on anatomic considerations of a smaller cross-sectional area of the pulmonary arteries, it seems reasonable to conclude that the severity of pulmonary hypoplasia would correlate with the severity of PHTN. However, a convincing relationship between lung size and PHTN has not been demonstrated in patients with CDH. Lung-to-head ratio (LHR) using ultrasound and percent-predicted lung volume (PPLV) using MRI are validated metrics of prenatal lung size in patients with CDH.[22–27] Additionally, postnatal tidal volume (V_T /kg) can be used as a surrogate for lung size, though this relationship is not as straightforward in neonates with CDH.[28] The purpose of this study was to assess the relationship between PHTN and these prenatal and postnatal measurements of lung size. We hypothesized that prenatal and postnatal measurements of lung size would predict the presence and severity of PHTN in neonates with CDH.

Methods

Study population and variables

After IRB approval, we retrospectively reviewed the medical records of all neonates born with isolated CDH at our institution between January 1, 2004 and May 31, 2015. Patients with severe chromosomal abnormalities and cardiac defects were excluded, as these conditions may confound the relationship between lung hypoplasia and PHTN. Patients were also excluded if they did not undergo echocardiography between day of life (DOL) 3–30. Data collected included demographics, prenatal lung measurements, postnatal ventilator settings, utilization of extracorporeal membrane oxygenation (ECMO), inhaled nitric oxide (iNO), or epoprostenol, and echocardiography (echo) data. To quantify the severity of CDH, each patient's predicted probability of survival was calculated according to the following equation derived by the CDH Study Group:

$$\text{Predicted probability of survival} = 1 - 1/[1 + \exp(-5.0240 + 0.9165(\text{BW}) + 0.4512 * \text{Apgar}_5)]$$

[29]

Prenatal lung measurements included observed-to-expected LHR (o:eLHR) and PPLV. Using ultrasound, the contralateral lung was measured in two-dimensions at the level of the atria and divided by head circumference to obtain LHR.[23] O:eLHR was calculated as observed LHR / expected LHR.[30] Fetal MRI total lung volumes were calculated for each patient from consecutive sections in two out of three imaging planes. An expected total lung volume was calculated for each patient based on the patient's EGA using the equation developed by Rypens et al: Expected Lung Volume (cc) = $0.0033 (EGA)^{2.86}$. [31] PPLV was then calculated from the equation: $PPLV = LV \text{ (observed)} / LV \text{ (expected)}$. Postnatally, the lowest reported V_T per kilogram within 12 hours of birth while on conventional ventilator support (i.e. excluding values obtained during high frequency oscillatory or jet ventilation [HFOV or HFJV] or ECMO) was recorded.

Endpoints

The primary outcome was severity of PHTN assessed by echo performed on DOL 3–30, provided the patient was not on ECMO. This echo timing was used because PHTN may be considered physiologic until DOL 3[32], and because our adopted institutional protocol included echocardiography at 4 weeks of age. Echoes done prior to DOL 3 were also recorded but not used to determine the primary outcome since, as mentioned above, significant PHTN would be expected during this early postnatal timeframe. Echo-derived measures of right ventricular systolic pressure (RVp) which equals pulmonary arterial systolic pressure (in the absence of outflow tract obstruction) were obtained using tricuspid valve regurgitation jet velocities when possible [$RVp = 4 \times (TR \text{ velocity})^2 + RAP$ (estimated)], or by comparing right ventricular pressure to systemic pressure by change in interventricular septal configuration during systole.[33] PHTN was then scored from 0–3: 0=no PHTN, 1= $\leq 1/2$ systemic pressure, 2= $1/2$ systemic-systemic, 3=suprasystemic. Secondary outcomes included development of clinically-relevant PHTN (defined as a PHTN score of 2–3) and use of inhaled nitric oxide (iNO) or epoprostenol.

Statistical analysis

Categorical and continuous variables were compared between patients who did and did not have clinically significant PHTN (i.e. grade 2–3) in a univariable analysis using the Chi-square test and Student's t-test, respectively. Categorical and continuous variables were compared by grade of PHTN severity (range, 0–3) in a univariable analysis using the Cochran-Mantel-Haenszel test and Jonckheere-Terpstra test, respectively. Non-parametric tests were used when appropriate. To evaluate the relationship between the different prenatal (o:eLHR and PPLV) and postnatal (V_T/kg) estimates of lung size, Pearson correlation coefficients were calculated. For the primary endpoint, proportional odds ordered logistic regression was used to assess association between each measure of lung size with grade of PHTN severity (range 0–3). To assess the association between each measure of lung size and the binary outcome of clinically relevant PHTN, logistic regression was employed. The logistic regression models were adjusted for estimated gestational age (EGA). Additional covariables were not included due to colinearity with the primary variable of interest (i.e. measure of lung size). Analyses were stratified by patients who did and did not require

ECMO. Logistic regression was also used to evaluate association between the measurements of lung size and utilization of treatment with iNO and epoprostenol. Statistical analysis was performed using SAS version 9.3 (SAS Institute, Cary, NC). A two-tailed p-value of <0.05 was considered significant.

Results

Two hundred fourteen patients with CDH were born during the study period. Of these 214, 53 were diagnosed postnatally and were excluded. After exclusion of patients with chromosomal anomalies, major cardiac defects, and those who did not undergo appropriately-timed follow-up echoes, 62 patients with isolated CDH were included in the study. Mortality of included patients was 32% (n=20). ECMO was utilized in 40 (65%) patients, iNO in 19 (31%), and epoprostenol in 13 (21%). Baseline patient characteristics are displayed in Table 1, grouped by presence (52%, n=32) or absence (48%, n=30) of clinically relevant PHTN documented on echo during DOL 3–30. Infants with clinically relevant PHTN (grades 2–3) had significantly lower predicted survival, 5-minute APGAR, o:eLHR, and PPLV, with higher mortality and rates of ECMO, iNO, and epoprostenol use. Fifty-three patients had an echo performed prior to DOL 2; of these, 49 (93%) had grade 2–3 PHTN. Among patients without clinically relevant PHTN on follow-up echo performed between DOL 3–30, 89% had an initial echo on DOL 0–2 that demonstrated clinically relevant (i.e. grade 2–3) PHTN.

Correlations between pre- and post-natal measures of lung size are displayed in Table 2. O:eLHR significantly correlated with both PPLV and V_T/kg . PPLV and V_T/kg did not significantly correlate with one another.

Among the overall cohort of 62 patients with isolated CDH, PPLV (odds ratio [OR]=0.92, 95% confidence interval [CI]=0.86–0.99, p=0.02), o:eLHR (OR=0.97, 95% CI=0.94–1.00, p=0.04), and V_T/kg (OR=0.92, 95% CI=0.86–0.99, p=0.02) were each significantly associated with the development of clinically relevant PHTN after adjusting for EGA. Within the subgroup of patients who required ECMO, PPLV (OR=0.87, 95% CI=0.76–0.99, p=0.03) and V_T/kg (OR=0.92, 95% CI=0.86–0.99, p=0.02) were significantly associated with clinically relevant PHTN.

PPLV (odds ratio [OR]=0.94 per 1 grade increase of PHTN severity, 95% confidence interval [CI]=0.89–0.98, p<0.01) and o:eLHR (OR=0.97, 95% CI=0.94–0.99, p<0.01) were also significantly associated with PHTN severity, whereas V_T/kg (OR=0.90, 95% CI=0.78–1.03, p=0.13) was not. Limited to patients on ECMO, the associations between PPLV (OR=0.92, 95% CI=0.84–0.99, p=0.03) and o:eLHR (OR=0.95, 95% CI=0.92–0.99, p=0.01) with PHTN severity were stronger. Among patients who did not require ECMO, no measure of lung size was significantly associated with development of clinically-relevant PHTN or PHTN severity (Table 3A–C). Finally, adjusting for EGA, PPLV and o:eLHR were significantly associated with utilization of iNO treatment (OR=0.90, 95% CI=0.83–0.98, P=0.01 and OR=0.94, 95% CI=0.91–0.98, P<0.01, respectively) and epoprostenol (OR=0.91, 95% CI=0.84–0.99, P=0.02 and OR=0.93, 95% CI=0.89–0.98, P<0.01, respectively), whereas V_T/kg was not (Table 4).

Discussion

CDH remains associated with significant morbidity and mortality despite advances in medical technology and therapy. An association between fetal lung size and the severity and clinical course of postnatal PHTN in infants with CDH is still not well-defined. We therefore aimed to better describe this relationship. Among infants with isolated CDH, we report significant associations between prenatal measure of lung size (i.e. o:eLHR and PPLV) and severity of PHTN as evaluated by echo during DOL 3–30. Additionally, o:eLHR and PPLV were significantly associated with the need for subsequent treatment with iNO or epoprostenol. These findings were driven by the ECMO population and disappeared when the analysis was limited to non-ECMO patients. Although V_T /kg was significantly associated with clinically-relevant PHTN, it was neither associated with severity of PHTN nor with the need for PHTN therapies.

It should also be stated that PHTN grade on echo prior to DOL 3 appeared unrelated to the persistence of PHTN later in life; 89% of patients with no clinically relevant PHTN between DOL 3–30 had an initial echo with grade 2–3 PHTN. In some cases these early elevated pulmonary pressures likely represented part of the normal transition from fetal to neonatal circulation, whereas in others it could have represented early pathologic PHTN that later resolved. This may, in part, explain why 50% of patients without clinically relevant PHTN from DOL 3–30 still underwent an ECMO run earlier in their hospital course.

Attempts to predict PHTN based on prenatal measurements have been made previously, with mixed results. Ruano et al., for example, noted correlation between PPLV and PHTN using 3-dimensional ultrasound.[34] However, in a systematic review, Russo et al. did not detect a relationship between prenatal markers of lung size (LHR, o:eLHR, and PPLV) and postnatal PHTN, but did establish a relationship between LHR, o:eLHR, and PPLV and postnatal ECMO requirement.[35] Other preliminary studies suggested a relationship between prenatal branch pulmonary artery size and PHTN.[36–38] A modified McGoon index (defined as [diameter of the right pulmonary artery + diameter of left pulmonary artery]/diameter of aorta as it passes through the diaphragm) was sensitive in predicting mild versus severe PHTN, but this study did not find an association between LHR, PPLV, and TLV, and the extent of postnatal PHTN.[38] Finally, mortality of CDH was found to decrease with increasing LHR, o:eLHR, and PPLV, as well as postnatal PHTN, suggesting that prenatal characteristics, correlated with the development and severity of PHTN, may also be used as a surrogate to predict overall survival.[39] In the aforementioned study, LHR, o:eLHR, and PPLV were associated with the presence of PHTN, defined as a pre- and post-ductal saturation difference greater than 10% consistent with a right to left shunt due to elevated pulmonary arterial pressures.[39] Our findings corroborate these conclusions and provide additional data to support the association between prenatal measurements and postnatal outcomes.

The persistence of PHTN in infants with CDH is a poor prognostic indicator. Lusk et al. demonstrated that persistence of PHTN past 2–3 weeks of life in infants with CDH was associated with increased rates of adverse pulmonary outcomes and decreased survival.[40] Of infants in whom PHTN resolved, the majority did so between 1 and 3 weeks of life, with

an average of 17 days to resolution. While these correlations between early postnatal characteristics and short-term clinical outcomes are useful in determining prognosis and developing treatment plans in the postnatal period, they do not allow for prenatal prognosis nor the planning of postnatal therapies.

In infants with CDH, a majority of therapies are directed towards alleviating reactive, reversible PHTN. Several therapies have been used to treat pulmonary hypertension in CDH patients, of which ECMO remains an excellent modality for treating refractory reactive pulmonary hypertension. ECMO allows the lungs to “rest,” avoiding barotrauma, while the pulmonary arterial vasoconstriction slowly decreases.[41–43] Though the pathophysiology is incompletely understood, this rest period may allow for resolution of over-activation of thromboxane synthase pathways.[42] Longer ECMO runs may, therefore, be efficacious for patients with the most severe PHTN.[44]

Several pharmacological modalities are also used to treat pulmonary hypertension, especially following ECMO therapy, including inhaled nitric oxide (iNO), phosphodiesterase inhibitors, prostaglandins, and endothelin receptor antagonists. The only prospective, randomized, and controlled trial of iNO treatment for CDH was the Neonatal Inhaled Nitric Oxide Study in 1997 which showed no benefit in terms of mortality and, in fact, higher ECMO utilization.[45] This study was underpowered to fully answer the question regarding the utility of iNO, but remains the only prospective study addressing iNO in patients with CDH. Despite the paucity of data, many centers use iNO and other adjunctive medications to treat PHTN in patients with CDH, often as a bridge to ECMO as well as following decannulation.[46]

Mechanistically, it is possible that there are two components of PHTN, an underlying fixed component based on lung size and a reactive physiologic component. The efficacy of each of the aforementioned therapies rests on the ability of each to overcome the reactive component of PHTN. The fixed component requires months of augmented lung growth to truly improve function and gas exchange. Even so, data suggest that long-term concomitant pulmonary vascular growth and development may never match lung growth, especially in more hypoplastic lungs at birth resulting in long-term V/Q mismatch.[47] The ability to overcome the reactive component of PHTN may also be dependent on the anatomical constraints of lung size. Nevertheless, physiologic factors still influence the natural history of PHTN, especially in the most severe cases.[48] Clearly this complex pathophysiology continues to make PHTN the Achilles heel of severe CDH. In either case, prenatal and postnatal lung size may be useful predictors of the severity of PHTN in patients with CDH.

There are several limitations to this study. First, as a retrospective analysis, the dataset remains limited to variables that were collected for the purpose of clinical management. As such, prenatal lung measurements and echocardiograms were not systematically obtained for all patients. This limited our study cohort significantly from the original pool of 214 patients. Secondly, there likely is some selective bias towards more severe CDH patients in this study given an ECMO utilization rate of 65% (our institutional ECMO utilization is approximately 40%[49]). The study was also limited by outcome measurement practices. Although cardiac catheterization is the gold standard for assessing pulmonary hypertension,

this method is highly invasive and was not routinely performed. Echo is a standard non-invasive technique to assess PHTN and was utilized in this study to determine the primary endpoint. Regarding PHTN measurement by echo, not all patients had tricuspid regurgitation from which to estimate RVp, and instead septal position was used as a surrogate for PHTN severity. While this approach may have limited accuracy, particularly in cases of mild-moderate PHTN, it is a widely accepted alternative strategy.[40] Furthermore, the timing of follow-up Echo varied within the 3–30 DOL range. In an attempt to minimize the effects of this variation, we utilized the Echo performed closest to DOL 30 whenever multiple Echos were performed. Regarding data analysis, it should be noted that many correlates with PHTN, though significant, demonstrated odds ratios close to 1.0. Though this may suggest that no one correlate is strongly predictive of development of PHTN, we would also point out that these odds ratios were generated based on incremental changes of 1 unit in factors such as PPLV and o:eLHR. It is not surprising that the odds of developing PHTN would only increase modestly, though significantly, for an increase in PPLV of 1; these odds ratios would be more pronounced had we used larger incremental units. Finally, generalizability is limited to patients with isolated CDH, and cannot therefore be applied to children with chromosomal anomalies or cardiac defects.

Conclusions

Prenatal lung size in infants with CDH, specifically as estimated by o:eLHR and PPLV, correlates with PHTN severity, with the strength of correlation accentuated in the ECMO population. These prenatal measures of lung size were also associated with utilization of iNO or epoprostenol. Prenatal evaluation can therefore be used to help predict postnatal PHTN, associated therapies, and clinical course.

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Table 1.

Baseline characteristics among 62 patients with congenital diaphragmatic hernia who underwent post-natal echocardiography, divided based on the presence or absence of clinically-relevant (i.e. grade 2–3) pulmonary hypertension (PHTN) between day of life (DOL) 3–30

<i>Variable</i>	<i>Clinically relevant PHTN</i>	<i>No clinically relevant PHTN</i>	<i>P</i>
Number (%)	32 (52)	30 (48)	
Female	14 (44)	11 (37)	0.57
EGA (weeks), median (IQR)	38.0 (36.9–39.3)	38.0 (37.0–39.1)	0.85
Birthweight (kg), median (IQR)	3.0 (2.5–3.2)	3.1 (2.7–3.4)	0.26
APGAR 5	5.0 (5.0–8.0)	8.0 (7.0–9.0)	<0.01
Right CDH	6 (19)	8 (27)	0.46
Predicted survival	48.2 (23.1–73.2)	75.3 (65.8–86.4)	<0.01
O:eLHR, median (IQR), n=61	41.6 (23.9–55.1)	45.8 (39.2–69.1)	0.04
PPLV, median (IQR), n=43	21.4 (16.0–30.2)	32.1 (24.5–41.8)	0.01
V_T/kg , ^a median (IQR), n=56	4.5 (2.5–6.9)	5.1 (4.6–7.5)	0.15
DOL 0–2 Grade 2–3 PHTN (%), n=53	26 (96)	23 (89%)	0.28
ECMO	25 (78)	15 (50)	0.02
iNO	15 (48)	4 (13)	<0.01
Epoprostenol	11 (35)	2 (7)	<0.01
Mortality	18 (56)	2 (7)	<0.01

Number (%) or median (IQR)

^aDay of life 1

CDH, congenital diaphragmatic hernia; *ECMO*, extracorporeal membrane oxygenation; *EGA*, estimated gestational age; *iNO*, inhaled nitric oxide; *IQR*, interquartile range; *o:eLHR*, observed-to-expected lung-to-head ratio; *PPLV*, %-predicted lung volume; *V_T/kg*, tidal volume per kilogram

Table 2.

Correlation between markers of lung size

<i>Variable</i>	o:eLHR		PPLV		V_T/kg	
	R Value	P	R Value	P	R Value	P
o:eLHR, n=51	--	--	0.49	<0.01	0.30	0.04
PPLV, n=43	0.49	<0.01	--	--	0.23	0.16
V _T /kg, ^a n=56	0.30	0.04	0.23	0.13	--	--

^aDay of life 1o:eLHR, observed-to-expected lung-to-head ratio; PPLV, %-predicted lung volume; V_T/kg, tidal volume per kilogram

Table 3A.Multivariable model of factors associated with grade of pulmonary hypertension (PHTN)^a

<i>Variable</i>	Overall		ECMO		No ECMO	
	<i>OR (95% CI)</i>	P	<i>OR (95% CI)</i>	P	<i>OR (95% CI)</i>	P
EGA (weeks)	1.31 (0.93–1.84)	0.12	1.39 (0.94–2.05)	0.10	1.23 (0.56–2.69)	0.61
PPLV	0.94 (0.89–0.98)	<0.01	0.92 (0.84–0.99)	0.03	1.00 (0.93–1.07)	0.98

^aPer increase of 1 point of PHTN grade^bAdjusted for estimated gestational age*DOL*, day of life; *ECMO*, extracorporeal membrane oxygenation; *EGA*, estimated gestational age; *PPLV*, %-predicted lung volume

Table 3B.Multivariable model of factors associated with grade of pulmonary hypertension (PHTN)^a

<i>Variable</i>	Overall		ECMO		No ECMO	
	<i>OR (95% CI)</i>	P	<i>OR (95% CI)</i>	P	<i>OR (95% CI)</i>	P
EGA (weeks)	1.29 (0.94–1.76)	0.11	1.43 (0.98–2.08)	0.06	1.20 (0.63–2.29)	0.58
oELHR	0.97 (0.94–0.99)	<0.01	0.95 (0.92–0.99)	0.01	1.00 (0.96–1.04)	0.86

^aPer increase of 1 point of PHTN grade^bAdjusted for estimated gestational age*DOL*, day of life; *ECMO*, extracorporeal membrane oxygenation; *EGA*, estimated gestational age; *o:eLHR*, observed-to-expected lung-to-head ratio

Table 3C.Multivariable model of factors associated with grade of pulmonary hypertension (PHTN)^a

<i>Variable</i>	Overall		ECMO		No ECMO	
	<i>OR (95% CI)</i>	P	<i>OR (95% CI)</i>	P	<i>OR (95% CI)</i>	P
EGA (weeks)	0.99 (0.75–1.31)	0.95	1.00 (0.73v1.38)	0.98	1.07 (0.51–2.27)	0.86
V_T/kg (DOL1)	0.90 (0.78–1.03)	0.13	0.98 (0.80–1.19)	0.81	0.86 (0.61–1.21)	0.37

^aPer increase of 1 point of PHTN grade^bAdjusted for estimated gestational age*DOL*, day of life; *ECMO*, extracorporeal membrane oxygenation; *EGA*, estimated gestational age; *V_T/kg*, tidal volume per kilogram

Table 4:Associations between measures of lung size and treatment with inhaled nitric oxide (iNO) or epoprostenol.^a

	<i>Odds Ratio (95% Confidence Interval)</i>	P
iNo		
<i>LHR</i>	0.94 (0.91–0.98)	0.003
<i>PPLV</i>	0.90 (0.83–0.98)	0.01
<i>V_T/kg</i>	0.92 (0.79–1.11)	0.39
Epoprostanol		
<i>LHR</i>	0.83 (0.65–1.06)	0.004
<i>PPLV</i>	0.83 (0.65–1.06)	0.02
<i>V_T/kg</i>	0.83 (0.65–1.06)	0.13

^aAdjusted for estimated gestational age

LHR, lung-to-head ratio; PPLV, %-predicted lung volume; VT/kg, tidal volume per kilogram