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Longitudinal Analysis of Pulmonary Function in Survivors of Congenital Diaphragmatic Hernia

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Abstract

Objective—To analyze longitudinal trends of pulmonary function test (PFT) in patients with congenital diaphragmatic hernia (CDH) followed in our multidisciplinary clinic.

Study design: This was a retrospective cohort study of CDH patients born between 1991 and 2013. A linear mixed effects model was fitted to estimate the trends of percent predicted forced expiratory volume in one second (FEV_{1pp}), percent predicted forced vital capacity (FVC_{pp}), and FEV₁/FVC over time.

Results: Of 268 CDH patients that survived to discharge, 119 had at least one PFT study. FEV_{1pp} ($P<0.001$), FVC_{pp} ($P=.017$), and FEV₁/FVC ($P=0.001$) declined with age. Compared with defect size A/B, those with defect size C/D had lower FEV_{1pp} by an average of 11.5% (95% CI: 2.9% – 20.1%; $P=0.010$). A history of oxygen utilization at initial hospital discharge also correlated with decreased FEV_{1pp} by an average of 8.0% (95% CI: 1.2% – 15.0%; $P=0.023$).

Conclusion: In a select cohort of CDH survivors, average pulmonary function declines with age relative to expected population normative values. Those with severe CDH represent a population at risk for worsening PFT measurements, who may benefit from recognition and monitoring for complications.

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Keywords

congenital diaphragmatic hernia; pulmonary function test; linear mixed effects model; FEV₁; FVC

Congenital diaphragmatic hernia (CDH) remains one of the most costly and challenging neonatal surgical conditions and requires a multi-modality approach in management both during initial hospitalization and in long-term follow-up [1–4]. Infants born with CDH suffer from altered pulmonary development that manifests as pulmonary hypoplasia and pulmonary hypertension [5–7]. Although many challenges remain, advancements in neonatal intensive care, extracorporeal membrane oxygenation (ECMO), and lung-protective ventilation techniques [4,8] have steadily improved early survival in CDH, which currently stands around 70% in most large population studies [9–11].

As an increasing number of CDH survivors reach adolescence and adulthood, new questions and challenges associated with the long-term care of these patients begin to arise. One important area is the potential progressive decline in pulmonary function over time. Although short-term studies have reported early evidence of pulmonary obstruction in CDH children [12,13], there remains a need to understand the long-term trajectory of pulmonary function test (PFT) in this unique cohort of patients. Given that neonatal lung injuries are emerging as a major risk factor for pulmonary morbidities later in life [14], it is reasonable to suspect that children with CDH may be susceptible to negative long-term outcomes, given significant alterations in pulmonary alveolar and vascular development early in life.

The Congenital Diaphragmatic Hernia Program at Boston Children's Hospital was established in 1991 and provides multidisciplinary care to one of the largest cohorts of CDH survivors in the world. Given that CDH population is a very heterogeneous group of patients with many clinical challenges, surveillance of pulmonary function has been a central component of our treatment approach. We focused on spirometry, a measure that any center can use to identify an at-risk patient, and performed a longitudinal evaluation of pulmonary function in CDH survivors followed at our institution. We hypothesized that pulmonary function abnormalities may be present early in life and potentially worsen through adolescence and early adulthood.

Methods:

This retrospective cohort study included CDH survivors born between 1991 and 2013 who were managed at our institution and had at least one PFT study before December 31, 2018. Exclusion criteria included late diagnosis of CDH, Morgagni-type hernia, and repair at an outside institution. After discharge, patients were followed long-term in the multidisciplinary CDH clinic with a consistent group of specialists. Spirometry was attempted at the first visit after 5 years of age, when patients were able to perform necessary forced exhalation techniques. Spirometry was performed on the SpiroAir Volumetric P.F.T. (Medisoft, Sorinnes, Belgium) using the American Thoracic Society (ATS)/European Respiratory Society (ERS) Task Force: Standardization of Lung Function Testing [15–17]. Forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC) were determined from the best out of three reproducible maneuvers when available. When a

patient had multiple PFT studies done in the same calendar year, only one with the highest FEV_{1pp} and acceptable technique was used.

Collected baseline characteristics for each patient included sex, inborn status, prenatal diagnosis of CDH, estimated gestational age (EGA) at birth, birth weight (BW), APGAR score at 1 and 5 minutes, presence of cardiac abnormality, and defect side. Variables that indicated the severity of CDH included CDH Study Group (CDHSG) defect size [18], liver position, presence of hernia sac, patch repair, ECMO utilization, and oxygen use at discharge from the index hospitalization. CDHSG defect size, which correlates well with clinical outcomes [18], was assessed at the time of surgical repair based on a grading scale of A-D for the smallest to the largest diaphragmatic defect.

Baseline characteristics were compared between patients who had at least one PFT and those who were never studied. Comparison of categorical variables was performed with a Chi-square or Fisher exact test and continuous variables were analyzed with a Wilcoxon rank-sum test. For patients who had a PFT done, a univariable linear regression model was used to identify the association between baseline variables and baseline percent predicted FEV₁ (FEV_{1pp}). FEV_{1pp} was calculated as a normalized value against the general population based on age, sex, and height [19,20]. Tested baseline variables included sex, inborn status, prenatal diagnosis, defect side, defect size, ECMO utilization, and oxygen need at discharge. Next, a multivariable linear regression model was fitted to identify significant predictors of baseline FEV_{1pp}. Variables that achieved a significance level of < 0.1 in the univariable analyses were entered into the multivariable model.

We considered the possibility of selection bias due to more frequent follow-up in more compromised patients. Adjustment for this selection bias was performed with inverse probability weight. First, baseline characteristics and PFT measurements were compared between children who had multiple PFT measurements and those who only had one study. Variables that showed significant differences were included in a multivariable logistic regression model to predict the probability of being selected for PFT follow-up. Inverse probability weight was created by inverting this probability and subsequently used for all longitudinal analyses. Application of inverse probability weight helped correct for selection bias by placing more weight on patients with multiple PFT studies who had similar characteristics to those lost to follow-up.

Due to the imbalanced nature of the study (ie, variable number of measurements per subject and variable duration in between consecutive measurements), a linear mixed effects model was used to estimate the trends of FEV_{1pp} and FEV₁/FVC over time. Covariates with a fixed effect in the model included age, defect size, defect side, ECMO use, and oxygen requirement at discharge. The regression model intercept and age also had a random effect, allowing each patient to have a different starting point and slope for PFT measurements.

Pulmonary obstruction was defined on spirometry as meeting both requirements of FEV_{1pp} < 80% and FEV₁/FVC < 80% [21]. A mixed-effects logistic regression model was used to predict the odds of having obstructive findings on spirometry. The model again included age,

defect size, defect side, ECMO use, and oxygen requirement at discharge, and intercept and age also had a random effect.

Further characterization of obstruction was performed with a bronchodilator challenge. Fixed obstruction was defined as obstruction with a less than 10% improvement in FEV₁ on bronchodilator challenge. Because bronchodilator challenge was only performed in a subset of patients, adjustment for selection bias with inverse probability weight was again performed for this analysis. Finally, this weight was included in a mixed-effects logistic regression model to predict the odds of being diagnosed with fixed obstruction on spirometry. Covariates of the model included age, defect size, defect side, ECMO use, and oxygen requirement at discharge, with the intercept having a random effect.

All statistical analyses were performed with SAS v. 9.4 (SAS Software, Cary, NC). In all analyses, a two-sided alpha level of 0.05 was used as the threshold for statistical significance. The study was approved by the Institutional Review Board at Boston Children's Hospital.

Results:

From 1991 to 2013, a total of 231 infants with CDH survived to discharge at our institution, representing a survival rate of 79%. Three patients were born before 32 weeks of gestation. Of these 231 patients, 119 had at least one complete PFT study. Compared with patients who had at least one PFT study, those without a PFT study had a lower rate of prenatal diagnosis (57.1% vs 71.8%, $P = 0.018$) and a higher proportion of transfer from an outside facility (50.7% vs 36.0%, $P = 0.034$). There was no difference in the median APGAR score, other congenital anomalies, rate of ECMO utilization, or proportion of large defect size between these two groups.

Age at the time of study ranged from 5 to 27 years. The number of PFT measurements per patient ranged from 1 to 15, with 90 patients (75.6%) having 3 measurements or less. 63 patients (52.9%) had PFT measurements past age 10, and 7 patients (5.9%) were tested until at least 20 years of age. Three patients had tracheostomy in early childhood, and all had been decannulated by age 3. Three patients underwent scoliosis surgery during the follow-up period. Among patients who had at least one PFT study, 74 had multiple studies and 45 had no follow-up (Table 1; available at www.jpeds.com). Bias was evident in selecting patients for PFT follow-up as there were significant heterogeneity between these two groups. In general, patients who had multiple PFT studies demonstrated more severe CDH baseline characteristics, as evidenced by a higher proportion of CDHSG defect size C/D (50.7% vs 20.0%; $P = 0.001$), liver-up (62.0% vs 28.9%; $P = 0.001$), and patch repair (67.6% vs 40.9%; $P = 0.007$). Patients with PFT follow-up were also more likely to utilize ECMO (43.2% vs 17.8%; $P = 0.005$) and require oxygen at discharge from the index hospitalization (41.9% vs 17.8%; $P = 0.008$). Of note, median baseline FEV_{1pp} was also significantly worse in patients who had repeated PFT studies (76.8% vs 91.7%; $P < 0.001$). In order to adjust for this selection bias, defect size, ECMO utilization, oxygen use at discharge, and baseline FEV_{1pp} were chosen as covariates for the inverse probability weight model.

We used linear regression models to identify significant predictors of baseline FEV_{1pp}. On univariable analysis, left-sided defect was associated with improved baseline FEV_{1pp} compared with right-sided defect ($P = 0.003$) (Table II). Conversely, defect size C/D ($P < 0.001$), ECMO utilization ($P < 0.001$), and oxygen requirement at discharge ($P < 0.001$) were all associated with decreased baseline FEV_{1pp}.

In the multivariable linear regression model, only defect size and oxygen requirement at discharge remained significant predictors of baseline FEV_{1pp}. Specifically, defect size C/D decreased FEV_{1pp} by 12.9% (95% CI: -21.7%, -4.2%; $P = 0.004$) and oxygen requirement at discharge was associated with a 8.7% decrease (95% CI: -15.9%, -1.5%; $P = 0.018$) in FEV_{1pp}.

A linear mixed effects model was used to describe the trends of PFT measurements over time. The average FEV_{1pp} of the cohort demonstrated a significant decline over time, at a rate of 0.8% per year (95% CI: -1.2%, -0.5%; $P < 0.001$) (Figure 1, A and B and Table 3). The mean FEV_{1pp} of fell from 80.9% at age 5 years of age to 68.8% at 20 years of age (Table 4; available at www.jpeds.com), with an expected FEV_{1pp} of > 80% and stable over time. Indicators of CDH severity also showed an effect on FEV_{1pp}. Defect size C/D lowered the mean FEV_{1pp} by 11.5% (95% CI: -20.1%, -2.9%; $P = 0.010$) and oxygen requirement at discharge was associated with an 8.0% decrease (95% CI: -15.0%, -1.2%; $P = 0.023$) in FEV_{1pp} (Table 3). CDH severity affected the baseline values for FEV_{1pp} but did not alter the rate of decline of future pulmonary function (Figure 1, C and D). This was also confirmed by non-significant interaction terms between age and indicators of CDH severity when they were introduced into the regression model.

Mean FVC_{pp} also demonstrated a significant decline over time, at a rate of 0.7% per year (95% CI: -1.3%, -0.1%; $P = 0.017$) (Figure 2, A [available at www.jpeds.com] and Table 3). The mean FVC_{pp} of the cohort fell from 90.4% at 5 years of age to 79.8% at 20 years of age (Table 4). As in FEV_{1pp}, mean FVC_{pp} is expected to be > 80% and stable over time in healthy children. Oxygen requirement at discharge lowered FVC_{pp} by an average of 9.6% (95% CI: -17.4%, -1.8%; $P = 0.017$), and defect size C/D was associated with a 9.5% decrease in FVC_{pp} (95% CI: -20.2%, 1.3%; $P = 0.084$).

FEV₁/FVC also decreased with age, showing a drop of 0.6% per year (95% CI: -1.0%, -0.3%; $P = 0.001$) (Figure 2, B [available at www.jpeds.com], Table 3, and Table 4). This trend in FEV₁/FVC fit with the previously reported trajectories of FEV_{1pp} and FVC_{pp}, where FEV_{1pp} demonstrated both lower baseline value and steeper decline over time. Defect size C/D was associated with a decrease of 4.8% in FEV₁/FVC (95% CI: -10.1%, 0.5%; $P = 0.074$).

In a mixed-effects logistic regression model, an increase of one year in age corresponded to a 33% increase in odds of being diagnosed with obstruction on spirometry (odds ratio (OR): 1.33; 95% CI: 1.11, 1.62; $P = 0.004$). The probability of obstructive findings on spirometry was 0.12 (95% CI: 0.03, 0.45) at 5 years of age and increased to 0.91 (95% CI: 0.51, 0.95) at 20 years of age (Figure 3, A).

Forty-seven patients underwent bronchodilator challenge. When fixed obstruction was defined by lack of significant reversibility after bronchodilator challenge, every year increase in age was associated with a 44% increase in odds of being diagnosed with fixed obstruction (OR: 1.44; 95% CI: 1.16, 1.79; $P = 0.002$). From age 5 to 20, the probability of a fixed obstruction diagnosis on spirometry increased from 0.01 (95% CI: 0.00, 0.05) to 0.65 (95% CI: 0.19, 0.94) (Figure 3, B).

Discussion:

In a cohort of CDH survivors followed at our institution, reduction in FEV_1 was apparent at an early age, especially in those with features of more severe CDH, such as large defect size and oxygen use at discharge from the index hospitalization. Over time, FEV_{1pp} , FVC_{pp} , and FEV_1/FVC continued to decline, although the rate of decline was independent of baseline CDH characteristics. As our CDH survivors reached adolescence and early adulthood, almost all of them demonstrated evidence of pulmonary obstruction on spirometry. Furthermore, among those who underwent bronchodilator challenge, the majority demonstrated evidence of fixed obstruction.

Of the common causes of neonatal respiratory failure, CDH has the strongest influence on the development of short- and long-term pulmonary morbidity [22]. Our findings are largely consistent with other reports on PFT in CDH survivors. Infant PFT, which can be done up to 3 years of age, has demonstrated air flow obstruction early in life among CDH survivors [12,13]. Similarly, the severity of pulmonary obstruction was also associated with the severity of pulmonary hypoplasia and pulmonary hypertension in the neonatal period [13,23,24]. The consistent association between disturbances in lung function with markers of both pulmonary hypoplasia and pulmonary hypertension highlights the intimate relationship between alveolar growth and maturation of the pulmonary vascular bed, both of which appear deficient in CDH survivors [25].

Perhaps the most notable result of this study was the longitudinal trend of PFT measurements over time. Although indicators of CDH severity clearly influenced the baseline PFT results, they had little effect on the trajectory of PFT measurements over time. In fact, the only significant determinant of PFT trajectory was time itself. On average, there was progressive decline in FEV_{1pp} and FEV_1/FVC in our study cohort, resulting in increasing probability of pulmonary obstruction with age. Most notably, the high incidence of fixed obstruction on spirometry found in this study was in direct contrast to previous studies of smaller size and shorter follow-up [26]. However, these results are consistent with our study on ventilation perfusion mismatch in the same cohort, in which we demonstrated a trend of increasing deficiency in relative perfusion of the ipsilateral lung with time [27]. Therefore, progressive decline in PFT measurements among CDH survivors may be related to an arrest in pulmonary parenchymal growth or may represent evolving emphysema, which predisposes these patients to future development of obstructive lung diseases.

Taken together, this cohort of CDH survivors demonstrate evidence of an “early below average, accelerated decline” in lung function trajectory, which has also been linked to other neonatal and childhood lung injuries, such as childhood asthma, bronchitis, hay fever,

pneumonia, smoke exposure, and especially bronchopulmonary dysplasia (BPD) [28–30]. Both CDH and BPD are characterized by sequela of lung hypoplasia, with features that include alveolar simplification, fixed obstruction of the airways, and a reduced vascular bed. Long-term pulmonary complications in CDH, therefore, may mimic the BPD model [31] and include vascular issues such as pulmonary hypertension, parenchymal changes such as emphysema, or musculoskeletal complications from scoliosis or chest wall deformities. Results of this study raised the concern that CDH survivors are on a unique trajectory for continually altered lung growth and abnormal physiology. As a result of significantly reduced baseline lung function, children with severe CDH may be at especially high risk for future development of chronic obstructive pulmonary diseases. These results, therefore, highlighted the need for dedicated adult programs that can provide both expert care to these patients as well as more complete data on their long-term outcomes.

The declining trend of PFT among CDH survivors in our study is more pronounced than previous studies [13,24,26,32], even after adjustment for selection bias. This could be partly explained by our longer study period (up to 23 years), which allowed for longer follow-up and a better opportunity to examine long-term manifestation of pulmonary function in CDH survivors. Additionally, the mortality rate of CDH at our center was 21% over the study period, which is significantly lower than the average reported in most large population studies [10,11]. As a result, our cohort of CDH survivors likely included a larger proportion of patients with higher disease severity, which could contribute to a steeper decline in longitudinal PFT measurements. However, it should be also be noted that despite this marked decline in PFT measurements, debilitating cardiopulmonary symptoms were rarely observed in our pediatric cohort. In a separate study that longitudinally assessed the functional status of CDH survivors followed in our clinic using a modified New York Heart Association Classification, the majority had normal cardiopulmonary function [27]. Class III and IV functional status, which included severe physical limitation with exercise, excessive work of breathing at rest, or oxygen dependence, was only seen in more than 10% of the assessments. Thus, although there was overall evidence of progressive decline in pulmonary function in this cohort, it appears that the majority of CDH survivors were able to adapt to these impairments and physical debilitation was only apparent in the most severe cases. However, the fact that even 10% of our patients had cardiopulmonary compromise highlighted the risk for those with a declining trajectory in PFT measurements to develop limitation in early adult years as well as the importance of continued surveillance.

We acknowledge limitations in our study. Although we attempted to adjust for selection bias, it was likely that residual bias for patients with greater disease severity still existed and our results are likely representative of a more severe subset of the entire population of CDH survivors. Among the potential residual confounding factors, we could not adjust for pulmonary hypertension (which was detected in 13 of our patients), as echocardiographic screening was not routine during the early years of the cohort.

Furthermore, longitudinal analysis of PFT in this study was presented without age-matched control subjects. Although the FEV₁ data were expressed as percent predicted, these numbers were derived from previously published normative values and did not take into consideration the potential differences in methodology and study site-specific populations.

Due to these limitations, any external generalization of these results to the entire population of CDH survivors needs to be taken with caution.

Finally, this study defined pulmonary obstruction entirely on spirometry studies. Because lung volume studies, which would allow for assessment of restrictive lung diseases and measurement of residual volume and total lung capacity, were only done sporadically in a subset of patients, the use of these additional parameters to diagnose obstruction would lead to a high degree of missing data and even further risk of selection bias. However, because spirometry is the most common and easily performed PFT, results of this study nevertheless reinforced its clinical value in the surveillance of pulmonary function among CDH survivors.

In conclusion, early deficiencies in pulmonary function strongly correlated with markers of CDH severity. Over time, the average pulmonary function in this cohort continued to decline, putting them at risk for obstructive findings on spirometry, especially in those with severe CDH and poor baseline pulmonary function. We suggest that as survival of CDH continues to improve, so does the need for multidisciplinary programs that can provide continued surveillance and expert care to these patients into their adult years. Our results highlight the utility of PFT in the surveillance of CDH survivors and the importance of identifying those with severe disease characteristics who are most at risk for further lung function deterioration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Trends of Percent Predicted Forced Expiratory Volume in 1 Second (FEV_{1pp}) over Time among Congenital Diaphragmatic Hernia (CDH) Survivors
Individual trends of FEV_{1pp} are displayed with Spaghetti plots (A). A linear mixed effects model was used to model the average trend of FEV_{1pp} of the entire cohort over time (B). Next, the average trends of FEV_{1pp} were stratified based on indicators of CDH severity, i.e. defect size (C) and oxygen requirement at discharge from the index hospitalization (D). Displayed are the regression lines and their associated 95% confidence interval (CI) bands.

Figure 2; Online Only. Trends of Percent Predicted Forced Vital Capacity (FVCpp) and FEV₁/FVC over Time among CDH Survivors

A linear mixed effects model was used to model the average trend of FVCpp (A) and FEV₁/FVC (B) of the entire cohort over time. Displayed are the regression lines and their associated 95% CI bands.

Figure 3. Probability of Pulmonary Obstruction and Fixed Obstruction over Time among CDH Survivors

A mixed-effects logistic regression model was used to estimate the probability of being diagnosed with pulmonary obstruction (A) and fixed obstruction (B) over time. Obstruction was defined as $FEV_{1pp} < 80\%$ and $FEV_1/FVC < 80\%$ on spirometry. Fixed obstruction was defined as obstruction with $< 10\%$ increase in FEV_1 with bronchodilator challenge. Displayed are the regression lines and their associated 95% CI bands.

Table 2.

Predictors of Baseline Percent Predicted Forced Expiratory Volume in 1 Second (FEV_{1pp}) in CDH Survivors

	Univariable Analysis			Multivariable Analysis		
	Effect Estimate	95% CI	P	Effect Estimate	95% CI	P
Defect size C/D	-17.62	(-24.87, -10.38)	< 0.001	-12.92	(-21.70, -4.15)	0.004
Oxygen at discharge	-16.21	(-23.62, -8.80)	< 0.001	-8.73	(-15.94, -1.52)	0.018
ECMO	-21.25	(-27.88, -14.62)	< 0.001	-5.82	(-14.46, 2.82)	0.184
Left-sided defect	14.38	(5.09, 23.66)	0.003	8.02	(-0.30, 16.34)	0.059
Male	-2.78	(-10.52, 4.97)	0.479			
Inborn	6.17	(-1.76, 14.10)	0.126			
Prenatal Diagnosis	-4.86	(-13.25, 3.53)	0.253			

Univariable and multivariable linear regression models were used to estimate the effect of different demographic and CDH characteristics on baseline FEV_{1pp}. Shown are effect estimate from the regression model and the 95% confidence interval (CI). ECMO: extracorporeal membrane oxygenation.

Table 3.

Trends of PFT Measurements in CDH Survivors

	FEV ₁ pp			FVCpp			FEV ₁ /FVC		
	Effect Estimate	95% CI	P	Effect Estimate	95% CI	P	Effect Estimate	95% CI	P
Age	-0.82	(-1.15, -0.49)	< 0.001	-0.70	(-1.28, -0.13)	0.017	-0.62	(-0.96, -0.28)	0.001
Defect Size C/D	-11.49	(-20.12, -2.86)	0.010	-9.46	(-20.24, 1.31)	0.084	-4.79	(-10.06, 0.48)	0.074
Oxygen at Discharge	-8.05	(-14.96, -1.15)	0.023	-9.62	(-17.43, -1.81)	0.017	0.66	(-3.10, 4.44)	0.724
ECMO	-6.98	(-15.50, 1.54)	0.107	-8.59	(-19.04, 1.86)	0.105	0.72	(-4.40, 5.85)	0.778
Left-Sided Defect	6.66	(1.60, 14.92)	0.113	7.12	(-2.15, 16.38)	0.129	1.49	(-3.43, 6.41)	0.545

A linear mixed effects model was used to model the effects of age and other baseline characteristics on FEV₁pp, percent predicted forced vital capacity (FVCpp), and FEV₁/FVC. Shown are effect estimate from the regression model and the 95% CI. ECMO: extracorporeal membrane oxygenation.