



# Predictors of early lung function in patients with congenital diaphragmatic hernia



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## ABSTRACT

**Purpose:** Long-term pulmonary outcomes of congenital diaphragmatic hernia (CDH) have demonstrated airflow obstruction in later childhood. We examined pulmonary function data to assess what factors predict lung function in the first three years of life in children with CDH.

**Methods:** This was a retrospective study of patients treated for CDH who underwent infant pulmonary function testing (IPFT) between 2006 and 2012. IPFT was performed using the raised volume rapid thoracoabdominal compression technique and plethysmography.

**Results:** Twenty-nine neonates with CDH had IPFTs in the first 3 years of life. Their mean predicted survival using the CDH Study Group equation was  $63\% \pm 4\%$ . Fourteen infants (48%) required extracorporeal membrane oxygenation (ECMO). The mean age at IPFT was  $85.1 \pm 5$  weeks. Airflow obstruction was the most common abnormality, seen in 14 subjects. 12 subjects had air trapping, and 9 demonstrated restrictive disease. ECMO ( $p = 0.002$ ), days on the ventilator ( $p = 0.028$ ), and days on oxygen ( $p = 0.023$ ) were associated with restrictive lung disease.

**Conclusion:** Despite following a group of patients with severe CDH, lung function revealed mild deficits in the first three years of life. Clinical markers of increased severity (ECMO, ventilator days, and prolonged oxygen use) are correlated with reduced lung function.

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Infants with congenital diaphragmatic hernia (CDH) suffer from significant morbidity and mortality. The combination of severe pulmonary hypoplasia and pulmonary hypertension, results in severe respiratory compromise [1,2]. As the survival of CDH has improved, interest has developed in long term morbidity of surviving patients [3].

Despite severe respiratory failure at birth, previous studies have suggested long term pulmonary function is relatively preserved in patients who survive outside of the neonatal period. A longitudinal study has suggested that adult survivors of CDH are left with only mild pulmonary function abnormalities [4]. In addition, Koumbourlis et al. showed that lung function and development normalize between 6 and 24 months of life [5].

In our institution, survivors of CDH are followed in a multidisciplinary clinic where infant pulmonary function tests (IPFT) are performed. The aim of this study was to assess pulmonary function of CDH patients in the first three years of life and identify factors associated with diminution of lung function.

## 1. Methods

We retrospectively reviewed all infants with a history of CDH who underwent infant PFTs between 2006 and 2012. All patients were initially cared for in the University of Michigan C.S. Mott Children's Hospital neonatal intensive care unit, and were subsequently followed in our multidisciplinary CDH clinic. All patients underwent infant PFTs in the first three years of life, ideally around one year of age, once patients were no longer requiring supplemental oxygen. This study was approved by our institutional review board (HUM00067303).

Data collected included prenatal data (defect side, liver position on fetal ultrasound, observed/expected lung-head ratios [O/E LHR], and fetal magnetic resonance imaging [MRI] percent predicted lung volumes [PPLV]) and perinatal data (gestational age at birth, birth weight, Apgar scores). In addition, we collected operative data (defect size, need for a patch, surgical approach, timing of repair) and data on the course of the hospitalization (need for high frequency ventilation, need for extracorporeal membrane oxygenation [ECMO], number of days on ECMO, ventilator days, days on oxygen, length of stay, and discharge medications).

Infant PFTs were obtained in the following manner: following sedation with 75–100 mg/kg of oral chloral hydrate, lung function was measured using the raised volume rapid thoracoabdominal compression technique and whole body plethysmography as

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**Table 1**

Demographic variables of 29 patients who underwent infant pulmonary function tests.

Variable	Result
N	29
Male	22 (76%)
Left-sided CDH	25 (86%)
Liver herniation	19 (65%)
Prenatal diagnosis	22 (76%)
Mean lung-to-head ratio (n = 23)	.42 ± .02
Mean percent predicted lung volume on MRI (n = 21)	.56 ± .03
Mean predicted survival using CDH Study Group equation	68.4% ± 4%
Mean age at PFT (weeks)	87.5 ± 6.3

previously described (Collins IPL, nSpire Health, Longmont, CO) [6–8]. Functional residual volume (FRC) was measured prior to performing maximal expiratory flow volume maneuvers. Forced vital capacity (FVC), forced expiratory volume in 0.5 s (FEV0.5), forced expiratory flows at 25% FEF25, 50% (FEF50), 75% (FEF75) and 85% (FEF85) of expired FVC (FEF25), and forced expiratory flow between 25% and 75% of FVC (FEF25–75) were measured. Only curves with FVC measurements within 10% of the highest baseline FVC were used for each maneuver. FRC, FVC and expiratory reserve volume were then used to calculate fractional lung volumes as previously described. The patient's measured length was then used to calculate the percent predicted expiratory forced flow and fractional lung volumes [6,8].

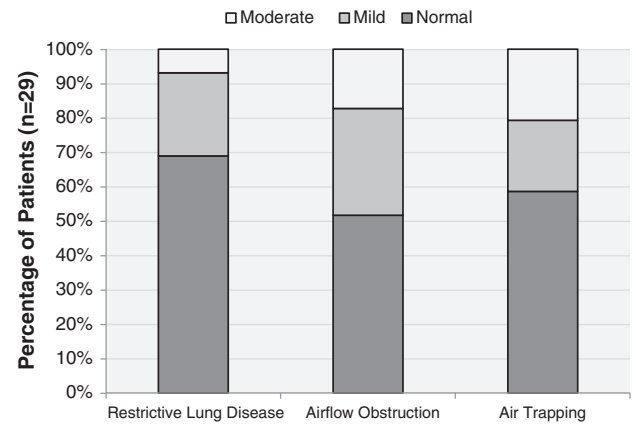
In interpreting the IPFTs, we classified the patients as having: 1) obstruction, which we defined as moderate if spirometry values of FEV were less than one standard deviation below normal; 2) restriction, which we defined as moderate if TLC was less than 70% of predicted; and/or 3) air trapping, which we defined as moderate if the RV/TLC ratio was greater than 140% of predicted. Normal values were obtained by previously published normative data for infants without lung disease [6].

We used the equation created by the CDH Study Group to predict survival at the time of birth in this patient population:

$$\text{probability of survival} = 1 - \frac{1}{1 + e^{(-5.0240 + 0.9165x + 0.4512y)}}$$

where  $x$  equals the patient's birth weight in kilograms and  $y$  equals the patient's Apgar score at 5 min of life to calculate each patient's predicted survival [9]. Since all these patients did survive to discharge, we used that predicted survival value as a surrogate for overall disease severity.

We analyzed the above data with descriptive statistics in Excel (Microsoft, Redmond, Wash). We then performed nonparametric comparative statistics (Kruskal–Wallis rank sum tests and Fisher

**Fig. 1.** Severity of varying forms of lung disease in 29 CDH patients based on infant pulmonary function tests.

exact tests) to examine the association between patient variables and the severity of lung disease using R (R Foundation for Statistical Computing, Vienna Austria).

## 2. Results

During the study period, one hundred twelve patients with CDH were cared for at our center. Of these, fifty one (45.5%) required ECMO. The predicted survival using the CDH study group equation referenced above was  $61\% \pm 2\%$ , with an actual survival of 72.3%. Of the eighty one survivors, thirty one (38.3%) required ECMO, with a predicted survival of  $67\% \pm 2\%$ . Twenty nine of these patients were identified as having undergone IPFTs and were included in the analysis. The mean predicted survival of the patients included in the study using the CDH study group equation was  $63\% \pm 4\%$ . Extracorporeal membrane oxygenation (ECMO) was required in 48% (14/29) of patients. There were 86% (25/29) left sided defects and 14% (4/26) right sided defects. Seventy six percent (22/29) of patients were diagnosed prenatally. Agenesis or near agenesis of the diaphragm was seen in 31% (9/29), 45% (13/29) required patch repair, and 21% (6/29) needed a temporary abdominal wall silo secondary to diminished abdominal domain (Table 1).

The mean number of ventilator days for the subjects was 25.7 days ( $\pm 16.6$ ). The mean number of days requiring supplemental oxygen was 87 days ( $\pm 139$ , range 7–555 days). Of the patients who required ECMO, the average duration was 10.3 days ( $\pm 5.4$ ).

At the time of discharge supplemental oxygen was required in 24% (7/29) of patients, 21% (6/29) required inhaled bronchodilators, and

**Table 2**

Association of restrictive, obstructive, and air-trapping lung disease with patient variables.

Variable	Restrictive disease				Obstructive disease				Air-trapping			
	Normal	Mild	Moderate	P	Normal	Mild	Moderate	P	Normal	Mild	Moderate	P
N	20	7	2		15	9	5		17	6	6	
Birth weight	3.1	3.5	2.7	.51	3.1	3.0	3.2	.68	2.9	3.1	3.4	.09
EGA	37.8	37.8	36.6	.29	37.9	37.7	37.2	.90	37.7	38.0	37.5	.82
Apgar 1 min	5.7	4.1	2.5	.14	5.1	5.0	4.8	.88	5.3	4.0	5.3	.65
Apgar 5 min	7.0	7.1	5.5	.40	7.1	7.0	6.2	.72	7.3	6.2	6.7	.39
Observed to expected LHR	41.8%	44.2%	53.0%	.68	44.7%	42.7%	41.0%	.80	44.5%	35.8%	47.9%	.37
PPLV on MRI	57.0	53.1	67.1	.50	58.9%	59.8%	47.3%	.30	54.5%	55.9%	61.0%	.80
Day of life at repair	7.6	7.9	11.0	.49	7.4	8.7	7.8	.46	8.1	7.3	7.8	.83
Ventilator-free days (out of 60)	39.3	28.3	16.0	.028	35.7	32.7	37.2	.72	37.2	32.0	31.7	.42
Days on oxygen	55.8	134.4	205.5	.023	109.8	74.7	29.8	.74	44.9	111.7	172.3	.17
Predicted Survival using CDHSG equation	69.5%	71.1%	49.3%	.45	70.9%	65.4%	65.6%	.77	69.4%	61.1%	72.0%	.63

P values from Kruskal–Wallis nonparametric analysis of variance. CDHSG = Congenital Diaphragmatic Hernia Study Group.

**Table 3**

Use of ECMO in the treatment of CDH and lung disease on Infant PFTs.

	Restrictive Lung Disease				Obstructive Lung Disease				Air-trapping			
	Normal	Mild	Moderate	P	Normal	Mild	Moderate	P	Normal	Mild	Moderate	P
ECMO												
No	14	0	1	<.001	9	3	3	.41	9	3	3	1.0
Yes	6	7	1		6	6	2		8	3	3	

P values from Fisher exact test. ECMO = extracorporeal membrane oxygenation.

14% (4/29) were discharged on inhaled steroids. Only two patients (7%) required sildenafil for treatment of pulmonary hypertension at the time of discharge.

The mean age at IPFT measurement was  $85 \pm 5$  weeks. Eleven subjects were on inhaled steroids at the time of testing. Airflow obstruction was the most common abnormality identified, as measured by reductions in FEF75 and FEF25–75, and was observed in 48% (14/29) of patients, 9 with mild obstruction and 5 with moderate obstruction. Air trapping, as measured by the RV/TLC ratio, was found in 41% (12/29) of patients, 6 with mild air trapping and 6 with moderate air trapping. Reduction in TLC, signifying restrictive lung disease, was seen in 31% (9/29) of patients, 7 with mild restriction and 2 with moderate restriction. These results are summarized in Table 2 and Fig. 1.

There was no association identified between any patient variables relating to prenatal measurements (LHR, MRI PPLV, O/E LHR) and any of the subtypes of lung disease. Number of days on the ventilator ( $p = 0.028$ ) and number of days requiring supplemental oxygen ( $p = 0.023$ ) were associated with restrictive lung disease on infant PFTs. The need for ECMO was compared across the 29 patients (Table 3). Need for ECMO was significantly associated with restrictive lung disease ( $p = <0.001$ ), but not significantly associated with obstructive disease or air-trapping. There was no significant association with defect side, liver position, prenatal diagnosis or patient sex with any type of lung disease.

### 3. Discussion

Over the past twenty years, survival has improved in patients with CDH. Predictably, improved survival of patients with severe CDH has resulted in increased long term pulmonary, gastrointestinal, and neurological morbidity. In this study, we were particularly interested in pulmonary outcomes in the first three years of life and identifying prenatal or postnatal factors associated with pulmonary outcome.

Previous studies have examined long term pulmonary function in patients with CDH. Koumbourlis et al. followed patients with serial PFT and found evidence of lung growth with only residual PFT abnormalities by 2 years of age [5]. Only 16% of their patient population required ECMO, however, which could indicate a higher threshold for ECMO utilization or a population with less severe disease in comparison to our group. Hayward et al. performed serial ventilation/perfusion scans on survivors with CDH and found there to be a persistent and progressive ipsilateral V/Q mismatch in many of these children, suggesting expansion of existing alveoli rather than new alveoli generation [10]. This was more common in those requiring patch repairs of the defect. The incidence of ECMO utilization in this patient population was 41%, making it more comparable to our study group.

Our study is unique in attempting to understand what factors are associated with lung function before three years of age in patients with CDH. We hypothesized that the severity of pulmonary hypoplasia assessed prenatally would be predictive of long term lung function. Although these factors (liver position, O/E LHR, and PPLV by fetal MRI) have been shown to be predictive of survival and need for ECMO [11,12]), we did not find an association with IPFT's. It is certainly possible that our sample size was too small to reach

statistical significance. Further studies will be required to more conclusively determine the relationship between prenatal measure of lung size and eventual lung function.

There are several limitations to our study. This was a retrospective study; therefore there is an inherent risk of bias. As some of these patients were not diagnosed prenatally, or were transferred in from an outside institution, there were some missing prenatal data for some of the patients. The IPFTs were not performed at exactly the same age, partly due to the requirement to be off supplemental oxygen for testing. Finally, there are some patients with CDH who did not undergo IPFT and may have been lost to follow up. We did review the ECMO utilization and predicted survival of all surviving patients and the subset that underwent IPFTs had higher ECMO utilization and lower predicted survival. Assuming these are sufficiently severe markers of disease severity, this suggests the subset of patients undergoing IPFTs were perhaps more severe than the group of patients who did not.

However, a few postnatal factors that are surrogate markers of CDH severity were found to be associated with abnormal pulmonary function. Not surprisingly, the use of ECMO was associated with restrictive lung disease. Restrictive lung disease had previously been shown to be associated with larger defect size, suggesting this indicates a greater degree of hypoplasia [13]. The ECMO utilization in this group is particularly high at 46%, but our institutional utilization over the past 10 years is approximately 40% (ECMO utilization has been reported from 11% to 61% of patients with CDH [14]). Our substantial rate of ECMO utilization likely reflects a severely ill population, as demonstrated by the overall predicted survival of this pool of 68%. Relatively high ECMO utilization is also likely a result of our preference to implement ECMO as soon as a “gentle ventilation strategy fails and before significant trauma occurs from high airway pressures [15,16].

Our patients also had a significant correlation between both ventilator days and duration of supplemental oxygen with restrictive lung disease on follow up. Previous studies have shown a similar association, thought to be related to trauma from high airway pressure and direct oxygen toxicity [17]. It is also possible, however, that this is simply a marker of patients with more severe hypoplasia at birth.

Our findings suggest that pulmonary function in the first three years of life is not substantially affected in survivors of CDH. The majority of our patients had mild or no pulmonary function abnormalities, even in late infancy. This is in agreement with a previously published study showing near normalization of pulmonary function tests by 24 months of age [5], as well as previous studies that had shown normal or mild disease in late childhood and early adulthood [18–20]. This is in contrast to other studies which had shown high incidences of respiratory symptoms in CDH patients, particularly those requiring ECMO. One study reports that 48% of this patient population has ongoing respiratory symptoms [21]. Our findings are pleasantly surprising since this particular cohort had severe disease as evidenced by high ECMO utilization, patch repair, need for abdominal wall silo, and the mean predicted survival of 63% using the CDH study group equation. We speculate that these findings suggest that lung protective strategies such as “gentle ventilation” and early institution of ECMO may be partly responsible for these relatively good early childhood outcomes.

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