Predictors of early lung function in patients with congenital diaphragmatic hernia

Tiffany Wright, Amy Filbrun, Benjamin Bryner, George Mychaliska *

University of Michigan, Ann Arbor, MI

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% ± 4%. Fourteen infants (48%) required extracorporeal membrane oxygenation (ECMO). The mean age at IPFT was 85.1 ± 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 multi-disciplinary 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 plethysmograhy as

* Corresponding author at: University of Michigan, C.S. Mott Children's Hospital, 1540 E Hospital Dr, SPC 4211, Ann Arbor, MI 48109. Tel.: +1 734 763 2072; fax: +1 734 936 9784.

E-mail address: mychalis@med.umich.edu (G. Mychaliska).

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 ration 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:

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

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
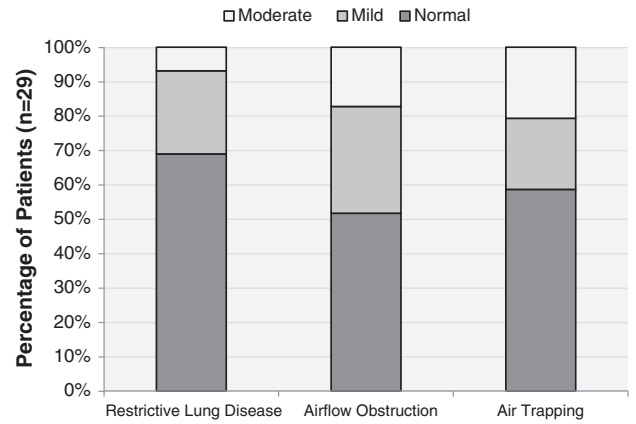

Fig. 1. Severity of varying forms of lung disease in 29 CDH patients based on infant pulmonary function tests.

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% ± 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% ± 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% ± 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 (± 16.6). The mean number of days requiring supplemental oxygen was 87 days (± 139, range 7–555 days). Of the patients who required ECMO, the average duration was 10.3 days (± 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.