

Prospective longitudinal evaluation of lung function during the first year of life after repair of congenital diaphragmatic hernia

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Abstract

Objective: To evaluate lung function and respiratory morbidity prospectively during the first year of life in patients with congenital diaphragmatic hernia (CDH) and to study the effect of extracorporeal membrane oxygenation therapy (ECMO).

Design: Prospective longitudinal cohort study

Setting: Outpatient clinic of a tertiary level pediatric hospital

Patients: The cohort of 43 infants included 12 patients treated with ECMO. Evaluation was at 6 and 12 months; 33 infants were evaluated at both time points.

Interventions: None

Measurements: Maximal expiratory flow at functional residual capacity ($V'_{\max_{\text{FRC}}}$) and functional residual capacity (FRC_p) were measured with Masterscreen Babybody (Viasys). Z-scores were calculated for $V'_{\max_{\text{FRC}}}$.

Main results: Mean $V'_{\max_{\text{FRC}}}$ values at 6 and 12 months were significantly below the expected values (mean Z-scores -1.4 and -1.5, respectively) without a significant change between both time points. Values did not significantly differ between ECMO and non-ECMO-treated patients. FRC_p values were generally high, 47% were above the suggested normal range, and did not change significantly over time. Mean FRC_p values in ECMO patients were significantly higher than in non-ECMO patients ($p=0.006$). The difference ($5.1 \text{ ml/kg} \pm 1.8 \text{ SE}$) did not change significantly between the two time points. Higher mean airway pressure and longer duration of ventilation were associated with higher FRC_p . None of the perinatal characteristics was associated with $V'_{\max_{\text{FRC}}}$. Mean weight Z-scores were significantly below zero at both time points ($p<0.001$). Mean weight Z-scores in ECMO patients were lower than in non-ECMO patients ($p=0.046$).

Conclusions: Infants with CDH have decreased expiratory flows and increased functional residual capacity within the first year of life. ECMO-treated CDH patients may have more respiratory morbidity and concomitant growth impairment. Close follow-up beyond the neonatal period is therefore required.

Key words: congenital diaphragmatic hernia; infant lung function testing; extracorporeal membrane oxygenation; bronchopulmonary dysplasia; respiratory morbidity.

Introduction

Congenital diaphragmatic hernia (CDH) occurs in 1 in 3000 live births and accounts for 8% of all major congenital anomalies (1). Many patients show lung hypoplasia and pulmonary hypertension requiring ventilatory support of variable duration. Conventional management includes different forms of mechanical ventilation (SIMV, IPPV, high-frequency oscillatory ventilation (HFOV), with or without inhaled nitric oxide). Infants with severe respiratory failure and high mortality risk will receive extracorporeal membrane oxygenation (ECMO) therapy in specialized centers. ECMO provides a cardiopulmonary bypass using minimal ventilator settings, potentially avoiding ongoing lung damage. Surgical repair of the diaphragmatic defect is delayed until stabilization is achieved and cardio respiratory condition has been optimized (2). These strategies have raised survival rates of CDH patients to almost 80% (3-4). However, survivors have high risk of respiratory morbidity through different stages of life. For example, ventilator induced lung injury and high concentrations of oxygen predispose newborns to develop bronchopulmonary dysplasia (BPD) (5).

Previous studies showed that ventilated CDH patients' lung volume was reduced during the immediate perioperative period and that their respiratory system compliance was low (6-7). A retrospective study in infants with CDH showed abnormal lung function indices in the first 6 months, which gradually normalized by 24 months (8). Recently, our group reported significantly higher lung volumes in the first year in ECMO-treated CDH patients than in infants who received ECMO for meconium aspiration syndrome (9). Results of studies investigating pulmonary sequelae of non-ECMO patients in late childhood and adolescence were indicative of persistent airway obstruction and increased airway responsiveness (10-12).

We prospectively evaluated CDH patients' lung function at 6 and 12 months of age and looked for a possible effect of ECMO treatment on respiratory morbidity. We also studied possible associations between clinical characteristics and lung function parameters and other factors contributing to respiratory morbidity.

Methods

A prospective longitudinal follow-up was conducted in all surviving patients with CDH admitted to the intensive care unit of the Erasmus MC - Sophia Children's Hospital between November 2004 and November 2008. (Flow chart, Figure 1). All patients were ventilated according to the principles of permissive hypercapnia and ventilatory support was provided either by conventional ventilation (Babylog 8000, Dräger Medical, Lübeck, Germany) or high-frequency oscillatory ventilation (Sensormedics, Bithoven, the Netherlands). All infants were treated according to a standardized treatment protocol (13). ECMO treatment was applied in case of reversible severe respiratory failure as described by Reiss et al (13). ECMO treatment always was of the veno-arterial type. Procedures and in- and exclusion criteria were described previously (9).

We recorded gestational age, birth weight, sex, side of the diaphragmatic defect, lung-to-head ratio (if available in case of a prenatal diagnosis) (14), position of the liver (intrathoracic or intra-abdominal, if available in case of a prenatal diagnosis), place of birth (inborn or outborn), initial ventilation mode (HFOV or conventional ventilation) and type of repair (primary or patch). Furthermore we recorded several indicators of illness severity: SNAP-II score during the first 12 hours (15), use of inotropics, use and maximal dose of inhaled nitric oxide (iNO), use of sildenafil, ECMO treatment, highest mean airway pressure (MAP), and duration of ventilatory support and supplemental oxygen provision. The presence and severity of BPD were determined as described by Bancalari (16).

The study was part of a follow-up programme for CDH patients in which lung function, growth and developmental parameters are regularly assessed until 18 years of age (17). The assessment protocol is the standard of care in the Netherlands. The Medical Ethical Review Board Erasmus MC stated that "Medical Research in Human Subjects Act (also known by its Dutch abbreviation "WMO") does not apply to this research proposal, since subjects are not being submitted to any handling, nor are there rules of human behaviour being imposed". Therefore IRB approval was waived. All parents were informed about the study and provided permission to use the data for research purposes. Lung function data were evaluated at the end of 2009.

Lung function

Lung function was measured at the ages of 6 and 12 months (corrected for prematurity), provided there were no signs of infection or acute respiratory symptoms. Patients were not mechanically ventilated and were independent of supplemental oxygen at the time of lung function measurement. Infants were sedated with chloral hydrate (50-75 mg/kg). Forced expiratory flow at FRC_p ($V'_{max_{FRC}}$), a measure of airway patency and compressibility, was determined by the end-tidal rapid thoracoabdominal compression technique (Masterscreen Babybody, Viasys, Hochberg, Germany). The mean $V'_{max_{FRC}}$ (ml/kg) of 3 to 5 technically acceptable measurements was calculated. All equipment and procedures complied with the guidelines of the ERS/ATS Task force on standards for infant respiratory testing (18). Regarding $V'_{max_{FRC}}$, we used the reference values provided by Hoo and colleagues (19). Z-scores were calculated as the difference between observed and predicted value divided by the residual standard deviation from the reference values for $V'_{max_{FRC}}$. Functional residual capacity (FRC_p) was measured by whole body plethysmography (Masterscreen Babybody, Viasys, Hochberg, Germany). The mean FRC_p (ml/kg) of 3 to 5 technically acceptable measurements was calculated. FRC_p was expressed in ml/kg as suggested by Hülkamp et al (20). The normal range suggested by those authors was 13 to 26 ml/kg. $V_{max_{FRC}}$ Z-scores and FRC_p (ml/kg) were the primary outcome measures.

Respiratory morbidity and physical growth

The infants were physically examined at both follow-up visits. Examination included measurement of height and weight, pulmonary auscultation, and neurological examination. Respiratory rate (RR) was measured during lung function assessment. The following factors were recorded: supplemental oxygen provision, episodes of wheezing, number of respiratory tract infections (RTI), therapeutic and prophylactic courses of antibiotic treatment, and use of inhaled bronchodilators and corticosteroids.

Dutch population data served as reference values for physical growth (21). Z-scores for weight and height were calculated using Growth Analyser version 3.5 (Dutch Growth Foundation). Z-scores < -1.96 (2.5th percentile of the reference population) were considered abnormally low; Z-scores > 1.96 (97.5th percentile of the reference population) were considered abnormally high. Z-scores for patients treated with ECMO were calculated separately.

The above-mentioned factors were the secondary outcome measures.

Data Analysis

Patient characteristics are presented as number of patients (percentage) or median (range). Univariate analyses were performed, using Chi-squared and Mann-Whitney U tests where appropriate, to evaluate differences between ECMO and non-ECMO patients. Anthropometric and lung function data are presented as mean (SD).

In this longitudinal study, the data are composed of repeated lung function measurements obtained in different individuals at two time points (six and twelve months of age). In the majority of patients, assessment at both time points was performed whereas in others only measurements at one time point were obtained. Since repeated measurements ANOVA allows for missing data at one time point, FRC_p , $V'_{max_{FRC}}$, $V_{max_{FRC}}$ Z-scores and Z-scores for weight and length were evaluated longitudinally using repeated measurements ANOVA, a method which allows for missing data at one time point (22). Possible associations between clinical characteristics and lung function parameters were also analysed using ANOVA. For this purpose, highest MAP and the duration of ventilation were transformed logarithmically to reduce the effect of outlying observations. To evaluate a possible influence of ECMO treatment on FRC_p , $V_{max_{FRC}}$ Z-scores and Z-scores for weight and length, we specifically performed ANOVA analyses adjusting for ECMO treatment. Possible associations between clinical characteristics between ECMO treated and non-ECMO treated patients were also evaluated in an ANOVA adjusting for age (6 and 12 months).

The significance level was set at $p < 0.05$. SPSS 17.0 (Chicago, Illinois) was used for the analyses.

Results

Between November 2004 and November 2008, 62 newborns with CDH had been admitted, of whom 48 had survived (77%). Two were lost to follow-up and 3 were clinically unstable or needed supplemental oxygen at the time of lung function assessment. Thus, 43 infants with CDH were included (Figure 1). Thirty-three infants were measured both at 6 and 12 months of age. Reasons for not completing both measurements were being awake during one of the measurements ($n = 4$), loss to follow-up ($n = 1$), recurrent RTI ($n = 1$). Furthermore, 4 infants whose first measurement was performed with different equipment were excluded. Baseline characteristics of the 43 infants are shown in Table 1.

Table 1. Baseline characteristics (n=43)

Data from the total group (n=43) and the subgroups of ECMO-patients (n=12) and non-ECMO patients (n=31). P-values are given for differences between the ECMO and non-ECMO group. Data are demonstrated as number (%) or median (range).*

Variables	.Total (n=43)	ECMO (n=12)	Non-ECMO (n=31)	p-value
Males	30 (70)	10 (83)	20 (65)	0.290
Left-sided defect	39 (91)	11 (92)	28 (90)	1.000
Prenatal diagnosis	27 (63)	4 (33)	23 (74)	0.032
Lung-to-head ratio	2 (0.9-3.5)	1.5 (1.3-2.4)	1.7 (0.9-3.5)	0.689
Intrathoracic liver position	9 (21)	2 (17)	7 (23)	0.702
Inborn	27 (63)	4 (33)	23 (74)	0.032
Gestational age, weeks	38.7 (33.6-41.4)	39.2 (36.9-41.4)	38.4 (33.6-41)	0.022
Birth weight, kilograms	3.0 (1.7-4.7)	3.0 (2.3-4.6)	3.0 (1.7-3.7)	0.524
High risk (intubated \leq 6 hrs after birth)	41 (95)	12 (100)	29 (94)	1.000
SNAPP-II score	21 (0-52)	37 (12-52)	16 (0-41)	0.095
Treatment with HFO ventilation	30 (75)	12 (100)	18 (58)	0.019
Patch repair	28 (65)	9 (75)	19 (61)	0.719
Treatment with iNO	24 (56)	12 (100)	12 (39)	<0.001
iNO maximum dose, ppm	20 (10-30)	20 (15-30)	20 (10-20)	0.574
Maximal mean airway pressure, cm H ₂ O	17 (10-29)	20 (17-29)	16 (10-20)	<0.001
Treatment with inotropics	39 (91)	12 (100)	27 (87)	0.563
Treatment with sildenafil	7 (16)	6 (50)	1 (3)	0.001
Bronchopulmonary dysplasia	16 (41)	7 (64)	9 (32)	0.150
Duration of mechanical ventilation, days	10.3 (0.7-53.4)	22.2 (8.5-53.4)	8.1 (0.7-51.6)	0.002
Duration of oxygen dependence, days	19.0 (3.0-141.3)	37.0 (9.6-141.3)	18.5 (3.0-104.5)	0.171

*Data from the subgroups of infants measured at 6 months (n= 36) and at 12 months (n=40) did not differ significantly and are not shown. iNO: inhaled Nitric Oxide, ppm: parts per million.

Lung function measurements

The median postnatal age at the two lung function tests was 29.9 weeks (range 26.0-37.7, n=36) and 56.1 weeks (range 49.3-66, n=40). The corresponding median age corrected for prematurity was 28.4 weeks (range 25-37.7) and 54.4 weeks (range 50.1-66.9). Reliable V'max_{FRC} measurements were obtained in 29 patients at 6 months and in 38 patients at 12 months. Reliable FRC_p measurements were obtained in 35 patients at 6 months and in 38 patients at 12 months. At 6 months 24 infants (73%) had a

RR \geq 35 breaths/min, of whom 17 (52%) \geq 40 breaths/min. At 12 months 18 infants (47%) had a RR of \geq 35 breaths/min, of whom 7 (18%) \geq 40 breaths/min.

Forty-seven percent of FRC_p measurements were $>$ 26 ml/kg (39% at 6 months and 55% at 12 months).

The mean FRC_p and mean Z-score of V'max_{FRC} did not change significantly over time. The results of the ANOVA analysis are presented in Table 2.

Table 2. Mean values of lung function parameters at 6 and 12 months

	6 months	12 months	P-value comparing the 2 time points
FRC _p (ml/kg)	28.1 (1.1)	28.7 (0.8)	0.518
V'max _{FRC} (Z-score) [†]	-1.4 (0.1) [†]	-1.5 (0.1) [†]	0.573
V'max _{FRC} (ml/sec)	108.0 (7.9)	153.9 (8.9)	<0.001
RR (breaths/min)	39.1 (1.2)	34.0 (1.2)	<0.001

Mean (SE) values from ANOVA are shown. FRC_p: functional residual capacity. RR: respiratory rate.

V'max_{FRC} (Z-score) [†]: $p < 0.001$ below the reference value (Z=0).

Associations between lung function parameters and clinical characteristics

Overall, a longer duration of ventilation was associated with higher FRC_p values at both 6 and 12 months ($p=0.001$). Doubling of the ventilation time resulted in a mean 1.9 ml/kg mean increase in FRC_p. Higher MAP was also significantly associated with higher FRC_p values at both time points ($p=0.002$). Furthermore, FRC_p values were significantly higher ($p=0.049$) and V'max_{FRC} Z-scores were significantly lower ($p=0.048$) in patients who received treatment with iNO ($p=0.049$).

Other significant associations between clinical characteristics and FRC_p values or V'max_{FRC} Z-scores were not found.

Lung function in ECMO patients

A total of twelve patients received ECMO therapy (see table 1) for a median of 7.1 days (range 3-12.1). The median day on which ECMO was started was the second day of life (range 1-4 days).

Table 1 lists clinical characteristics for both ECMO and non-ECMO patients. The former were less often prenatally diagnosed ($p=0.032$), less often inborn ($p=0.032$), had a higher median gestational age at birth ($p=0.022$), were more often treated with iNO ($p<0.001$) and sildenafil ($p=0.001$), had a higher median maximal mean airway pressure ($p<0.001$), were more often treated with HFO ($p=0.019$) and were ventilated for a longer time ($p=0.002$) than non-ECMO patients.

At both time points, mean FRC_p values differed significantly between ECMO- and non-ECMO-treated patients ($p=0.006$, Figure 2). This difference ($5.1 \text{ ml/kg} \pm 1.8 \text{ SE}$) did not significantly change between the two time points ($p=0.625$). In ECMO patients, mean (SE) $V'_{\max_{FRC}}$ Z-scores at 6 and 12 months were $-1.52 (0.31)$ and $-1.54 (0.25)$ respectively. Mean (SE) $V'_{\max_{FRC}}$ Z-scores at 6 and 12 months were $-1.41 (0.14)$ and $-1.49 (0.15)$ in patients who did not receive ECMO therapy. These did not differ significantly ($p=0.781$).

To further evaluate possible effects of clinical characteristics and ECMO therapy on FRC_p values, these characteristics were entered in the ANOVA models together with the factor ECMO. When adjusted for duration of ventilation or highest mean airway pressure, the difference in FRC_p values between ECMO and non-ECMO patients was not significant anymore ($p=0.108$ and $p=0.369$ respectively). No other significant associations between baseline characteristics and FRC_p values were found when adjusted for ECMO.

ECMO and BPD

Sixteen patients developed BPD (41%, missing=4, see table 1). At both time points, BPD patients' mean FRC_p was significantly higher than that of the non-BPD patients ($p<0.001$, Figure 3). This difference ($6.2 \text{ ml/kg} \pm 1.5 \text{ SE}$) did not significantly change between the two time points ($p=0.585$). ANOVA did not reveal a significant effect of BPD on $V'_{\max_{FRC}}$ Z-scores ($p=0.159$).

Seven of the 11 ECMO-treated patients developed BPD (1 missing) versus 9 of the 28 non-ECMO patients (3 missing, $p=0.15$, see table 1). Simultaneous evaluation of BPD and ECMO resulted in a significant effect of BPD on FRC_p ($p=0.001$, difference: 3.2 ml/kg lower in no BPD). The effect of ECMO was larger in this combined analysis (difference: 5.4 ml/kg lower in no ECMO) but did not reach statistical significance ($p=0.066$).

In Figure 4, individual FRC_p measurements are shown for the 4 combinations of ECMO/non-ECMO and BPD/non-BPD. Data obtained at 6 and 12 months were clustered because there were no significant differences between the 2 time points.

Respiratory morbidity and physical growth

At 6 months, 4 patients (12%) had received at least one therapeutic course of antibiotics; the same was true for 7 patients (19%) at 12 months. One child used antibiotics daily for 12 months to prevent recurrent respiratory tract infections. Two (6%) and 5 (14%) patients used bronchodilators and/or inhaled corticosteroids at 6 and 12 months, respectively. At 6 and 12 months, 12 (28%) and 6 patients (14%) respectively had an abnormally low weight. Mean weight Z-scores were -1.01 (0.22) and -1.10 (0.18) at 6 and 12 months, respectively, significantly below the norm ($Z=0$, $p < 0.001$ at both time points). At both 6 and 12 months, weight Z-scores in ECMO-treated patients (6 months: -1.61 (0.37) and 12 months: -1.59 (0.32)) were significantly lower than in patients without ECMO (6 months: -0.83 (0.22) and 12 months: -0.82 (0.20), $p=0.047$). Mean height Z-scores were 0.02 (0.18) and 0.07 (0.16) at 6 and 12 months, respectively. Height Z-scores were not significantly different from normal at 6 and 12 months ($p=0.9$ and $p=0.6$ respectively). At both time points, height Z-scores did not differ significantly between patients with and without ECMO.

Discussion

This prospective longitudinal study revealed that FRC_p in patients with CDH was generally above the expected range and did not change significantly from 6 to 12 months. Forced expiratory flows were below the expected value and also did not change. ECMO-treatment was associated with significantly higher FRC_p . Presence of BPD, higher MAP and longer duration of ventilation were associated with higher FRC_p . None of the perinatal characteristics was associated with $V'max_{FRC}$.

Two studies by other groups reported reduced forced vital capacity and impaired maximal expiratory flows in neonates with CDH who were still on mechanical ventilation during lung function assessment (6-7). In these studies, measurements were taken within the first weeks of life and the findings therefore cannot be compared to our findings in older and spontaneously breathing infants. A retrospective evaluation in 56 CDH patients showed that FRC_p Z-scores, measured with the nitrogen washout technique, were initially below average but increased after the first 6 months of life; $V'max_{FRC}$ was below average throughout the first year of life (8). A study using the sulphur hexafluoride wash-in/wash-out technique found similar FRC_p levels in 13 CDH patients and in age-matched healthy controls (23). Earlier, our group found higher FRC_p levels in ECMO-treated CDH patients than in infants who needed ECMO-support for meconium aspiration syndrome (9). These findings on FRC_p are in line with the present findings.

In the present study, FRC_p values were generally above the expected range. This is likely to be due to the lung hypoplasia that is inherent to CDH (24-27). Repair of CDH is usually followed by compensatory hyperinflation of the ipsilateral and/or the contralateral lung to fill the space previously occupied by abdominal organs (8). Helms and Stocks, however, found normal to low FRC_p in infants aged up to 8 weeks after operative repair of CDH (28). They argued that normal lung volume does not necessarily imply normal intrauterine lung development. Indeed, normal lung volume later in infancy (29) may be the result of alveolar distension and even of destructive emphysema of a hypoplastic lung (24, 30). Nagaya and co-workers, using computed tomography scans and perfusion scintigrams in infants following surgical repair of CDH and ECMO treatment, found ipsilateral lung volumes that were 61% of contralateral lung volumes at 3 months and had increased to 88% at 3 years of age (31). Perfusion of the affected side remained low, or decreased to below the initial value. These authors concluded that the ipsilateral lung apparently may have little ability to develop arterial branches and that enlargement of lung volume may depend on overexpansion or progressive emphysema, rather than on an increase in lung tissue (31).

Hayward and co-workers suggested that expansion of already existing alveoli and not an increase in the number of alveoli explained most of the lung growth in their CDH population 0.1-13 years(32). Thus, the normal, near-normal or elevated FRC_p values in our study are more likely to reflect hyperinflation than true lung tissue growth. FRC_p values did not increase from 6 to 12 months, so there seems to be no progressive hyperinflation. Indeed, studies in older children after repair of CDH showed mildly increased residual volume and mild airway obstruction (10-12).

The question remains whether increased FRC_p levels in CDH result from abnormal lung development or from lung damage due to barotrauma and hyperoxia. Most studies on lung function in BPD patients without CDH concern prematurely born neonates. As CDH patients are mainly born at term, findings are hard to compare. Studies on term born infants with BPD are scarce. However, Hofhuis and co-workers found that FRC_p levels at 6 and 12 months in in ECMO-treated CDH patients were significantly higher than those in neonates treated with ECMO for meconium aspiration syndrome (MAS) (9). Fifteen of the 25 MAS patients (60%) in that studied developed BPD (personal communication). This suggests that the elevated FRC_p values in our population resulted from abnormal lung development in CDH patients rather than from the neonatal intensive care treatment. This assumption is supported by the study of Beardsmore and co-workers who found similar FRC_p levels in term born neonates treated with ECMO or with conventional ventilation (33).

It could be argued that plethysmography in CDH patients with or without BPD in the present study may not be suitable to evaluate alveolar functional recovery. On the other hand, gas dilution FRC measurements also has limitations, and underestimates lung volumes as gas diffusion is suboptimal in airways with an elevated resistance. Hence, we propose that follow-up should include both lung function studies and lung imaging to evaluate the evolution of lung volume in CDH patients.

In the present study, FRC_p in ECMO-treated patients was higher than in the other patients. We may speculate that ECMO treatment increases the chance of survival in case of CDH with more severe lung hypoplasia and/or persistent pulmonary hypertension, and consequently a higher respiratory morbidity and more hyperinflation of the lungs (9). Indeed, after failure of conventional ventilation, HFO ventilation was used more frequently in the ECMO treated group. Also, total ventilation time and MAP were significantly higher in the ECMO treated group. In the ECMO treated group, 64% developed BPD versus 32% in the non-ECMO treated group and although this difference did not reach statistical significance, it indicates more severe respiratory problems which is associated with higher FRC_p . A study by Bernbaum

et al. reported a 63% incidence of BPD at discharge in survivors of CDH who underwent ECMO-procedure (34). This incidence is the same as we found in our study. Also ECMO-treated patients received more often iNO and sildenafil in order to reduce pulmonary hypertension.

The decreased maximal expiratory flows in our study are in agreement with findings from similar studies in CDH patients (6-8, 35). Abnormal airway size or alveolar architecture may play a role here together with airway damage from mechanical ventilation. We found neither significant differences in forced expiratory flows between patients treated conservatively or with ECMO, nor between patients who did or did not develop BPD. Therefore, it seems that differences in FRC_p cannot be explained by differences in airway obstruction only.

Although 41% of the patients developed BPD, only few suffered from respiratory tract infections requiring antibiotic treatment. Only few patients had wheezing and/or dyspnea requiring inhaled medication. We speculate that an increased airflow obstruction is indicative of abnormal airway structure and fibrosis as a result of lung injury rather than of increased airway responsiveness. All patients showed impaired growth during the first year of life, especially the ECMO-treated patients with weight Z-scores below average.

A potential limitation of our study was that we were not allowed to examine healthy controls, as sedation of healthy infants for research purposes is not permitted in the Netherlands. Therefore, we had to use reference values published by others. We expressed FRC_p values in ml/kg. The earlier reference equations to compute FRC_p into Z-scores are perhaps not entirely appropriate for data obtained with the newer equipment. We therefore expressed results as ml/kg, which is acceptable in the neonatal period, as the regression of FRC_p on weight is relatively linear and passes close to the origin (36). Until new reference data are available, users of new equipment would do well to interpret results cautiously. The normal range of FRC, suggested by Hülkamp et al, is 13-26 ml/kg, mean 19.6, SD 3.4 (20). Regarding $V'_{max_{FRC}}$, we used the reference values provided by Hoo and colleagues. These reference values are based on a large representative population of healthy infants (19) and have been used by others using similar equipment as we did (37). Another limitation was the lack of well defined parameters to assess the severity of pulmonary hypertension and the effect on cardiac function by cardiac ultrasound retrospectively. A possible relation between lung function parameters in the first year of life and severity of pulmonary hypertension shortly after birth could therefore not be established. Also, we did not evaluate pulmonary hypertension and a possible effect on lung function by cardiac ultrasound during follow-up.

In summary, we found evidence of lung hyperinflation and impaired lung growth in CDH survivors after ECMO-treatment. Long-term monitoring of these patients' lung function evolution is recommended.

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FIGURE LEGENDS

Figure 1: Flowchart

Figure 1. *2 patients were lost to follow up, 3 patients still had oxygen therapy at the time of lung function assessment and therefore measurements could not be performed

CDH: congenital diaphragmatic hernia

PPHN: therapy resistant persistent pulmonary hypertension of the neonate

MCA: multiple congenital anomalies

Figure 2 : FRC_p at 6 and 12 months in ECMO and non-ECMO treated CDH patients

FRC_p (ml/kg) measurements in CDH patients who were treated with ECMO (2 panels left side; ECMO) and in those who were not treated with ECMO (2 panels right side; no ECMO) at the age of 6 and 12 months. Bars denote mean values from repeated measurements ANOVA. Data shown at the bottom represent means with standard error (SE) between parentheses. Mean levels at both 6 and 12 months did not significantly differ between ECMO and non-ECMO treated patients (both $p > 0.60$).

Figure 3: FRC_p at 6 and 12 months in CDH patients with and without BPD

FRC_p (ml/kg) measurements in CDH patients who developed BPD (2 panels left side; BPD) and those who did not develop BPD (2 panels right side; no BPD) at the age of 6 and 12 months. Bars denote mean values from repeated measurements ANOVA. Data shown at the bottom represent means with SE between parentheses. Mean levels at both 6 and 12 months did not significantly differ between patients with and without BPD (both $p > 0.30$).

Figure 4: FRC_p measurements in four different groups of CDH patients

FRC_p (ml/kg) measurements of CDH at 6 and 12 months. Closed symbols represent ECMO-treated newborns; open symbols represent non-ECMO treated patients. BPD is indicated as circles; no-BPD as triangles. Thus, 4 different groups are shown. Bars denote mean values from repeated measurements ANOVA. Data shown at the bottom represent means with SE between parentheses.

* mean level in this group significantly differed from that in the no ECMO/no BPD group (both $p \leq 0.003$).

Other differences between groups were not significant.

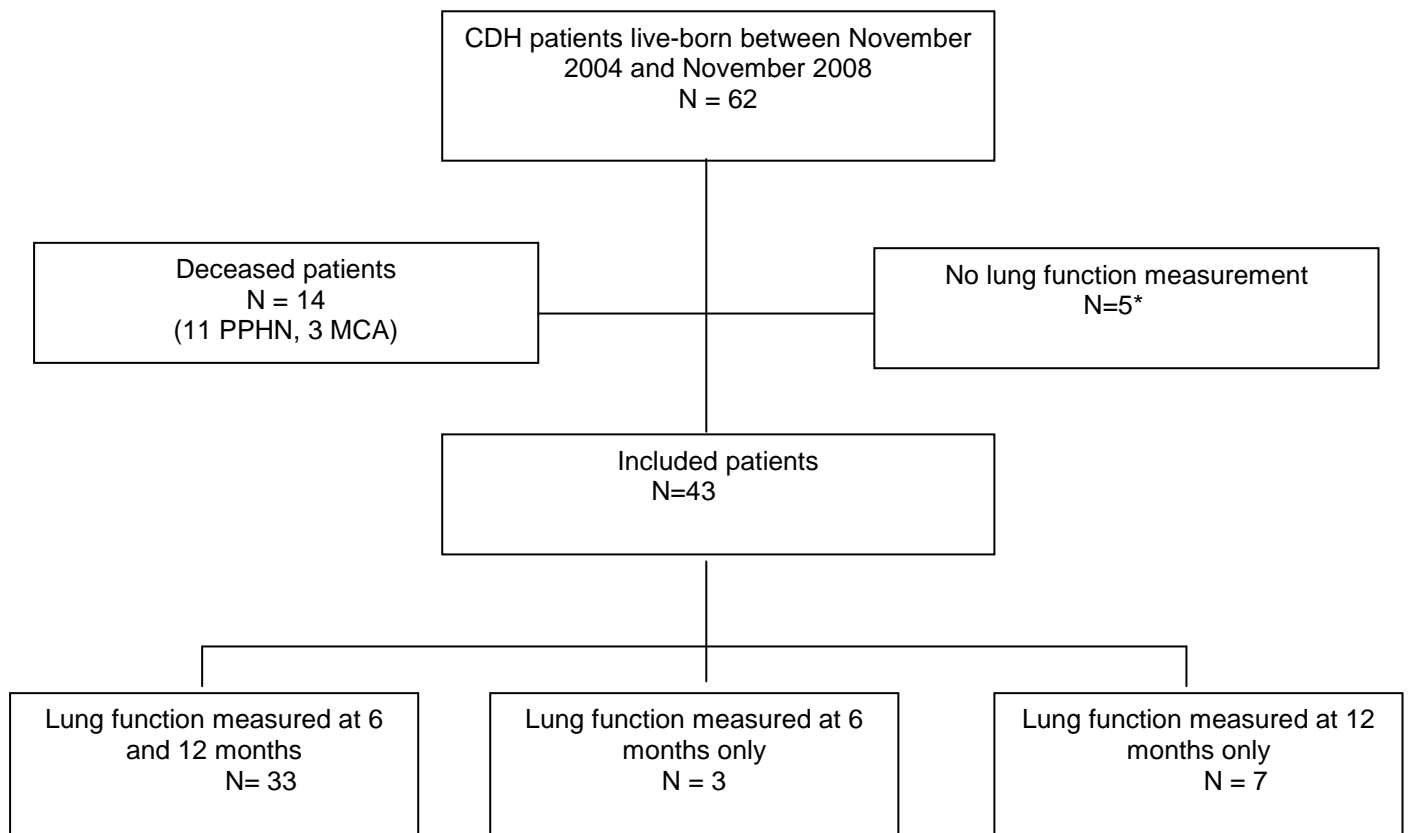
Figure 1

Figure 2

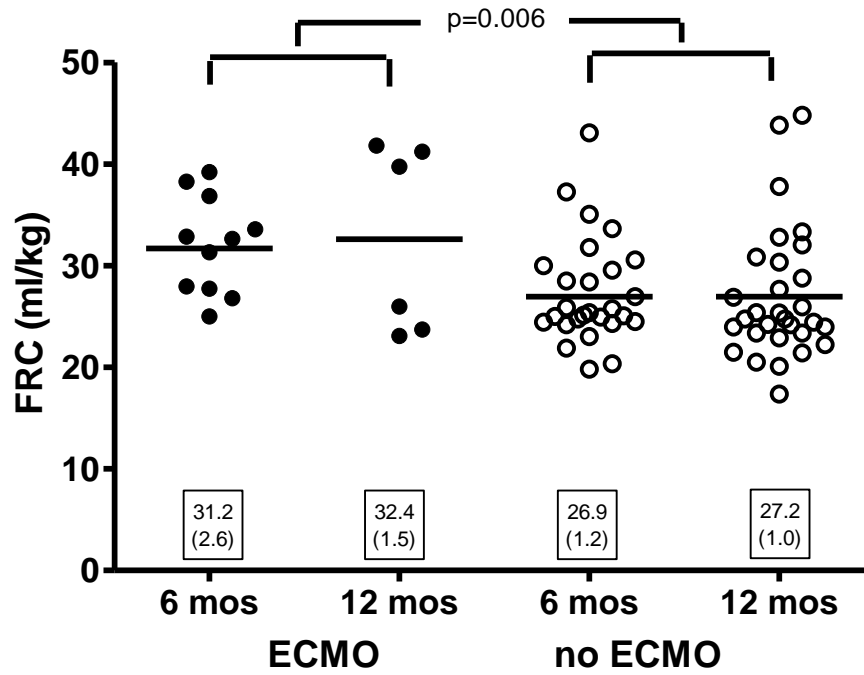


Figure 3

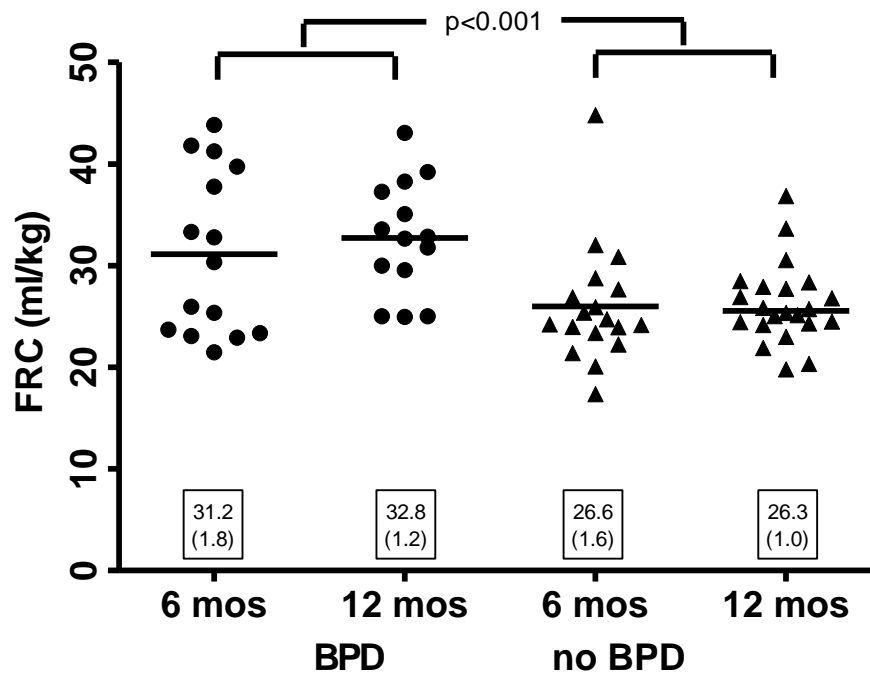


Figure 4

