Peer reviewed article

The pulmonary outcome of long-term survivors after congenital diaphragmatic hernia repair

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Summary

Background: Congenital diaphragmatic hernia (CDH) represents a chronic condition with significant pulmonary and non-pulmonary complications. The main aim of the present study was to determine the pulmonary outcome in a group of long-term survivors of CDH.

Methods: Clinical records of 46 patients with CDH admitted to the University Children's Hospital Zurich between 1991 and 2001 were reviewed retrospectively. Survivors underwent clinical examination, lung function tests and measurements of exhaled nitric oxide.

Results: 30 of 46 (65%) patients survived after repair of CDH and 19 children participated in a follow-up study at the mean age of 7.9 (2.8) years. At least one wheezy episode requiring inhaled bronchodilators was reported by 9/19 (47%) children and 4/19 (21%) children complained of recurrent wheezy episodes.

Nine children showed lung function impairment in spirometry as well as in oscillatory resistance. Neither duration of assisted ventilation nor the length of hospitalisation appeared to correlate with lung function. Exhaled nitric oxide was within normal range in our group of CDH survivors.

Measurement of respiratory system resistance using a forced oscillation technique detected those CDH survivors, who showed abnormal pattern in spirometry. However, no correlation between oscillatory resistance and specific airway resistance measured by whole body plethysmography was found.

Conclusions: Despite the presence of rather insignificant symptoms, we found mild to moderate pulmonary functional impairment in children surviving CDH repair.

Key words: congenital diaphragmatic hernia; lung function; forced oscillation technique; exhaled nitric oxide

Abbreviation list

BPD	bronchopulmonary dysplasia
CDH	congenital diaphragmatic hernia
ECMO	extracorporeal membrane oxygenation
ERS	European Respiratory Society
FEV_1	Forced expiratory volume in 1st second
FOT	forced oscillation technique
FVC	forced vital capacity
GER	gastroesophageal reflux
HFOV	high-frequency oscillation ventilation
iNO	inhaled nitric oxide
ITGV	intra-thoracic gas volume
MCH	methacholine
MEF_{75} MEF_{50} MEF_{25}	maximum expiratory flow at 75%, 50% and at 25% of vital capacity
PEF	peak expiratory flow
R tot	total resistance
Rrs	resistance of respiratory system
RV	residual volume
SR tot	total specific airway resistance
TLC	total lung capacity
VC	vital capacity
Xrs	reactance of respiratory system

This study was performed at: University Children's Hospital, Steinwiesstrasse 85, Zurich, Switzerland.

No financial or other potential conflicts of interest exist.

Introduction

Congenital diaphragmatic hernia (CDH) refers to a defect in the diaphragm that allows abdominal organs to move into the chest cavity. Depending on the timing of the herniation and the volume of abdominal organs involved, this defect has the potential to disrupt normal lung development. Delayed operative repair [1], inhaled nitric oxide (iNO) [2], high-frequency oscillation ventilation (HFOV) [3], gentle ventilation with permissive hypercapnia [4] and extracorporeal membrane oxygenation (ECMO) [5] have resulted in an increased survival. Chronic pulmonary disease, feeding problems including gastroesophageal reflux [6], orthopaedic problems such as scoliosis [7] and neurological complications [8] represent the major causes of morbidity in CDH survivors today.

The aim of the present study was to evaluate the long-term pulmonary morbidity in children who had undergone repair of a CDH during a ten-year period in a tertiary centre in Switzerland.

Materials and methods

Subjects

Clinical records of all children born between 1991 and 2001 with the diagnosis of CDH and referred to the University Children's Hospital Zurich were reviewed retrospectively. Data collected included gestational age, gender, birth weight, Apgar score, duration of assisted ventilation, age at surgery and length of hospitalisation. Five patients with chromosomal aberration as well as four patients with diaphragmatic relaxation or Morgagni hernia were excluded.

The Medical Ethics Committee of the University Hospital Zurich approved the study and written informed consent was obtained prior to testing from all parents.

Long-term follow-up

A questionnaire pertaining to respiratory symptoms in the first three years of life, history of asthma and allergy, gastroesophageal reflux requiring pharmacological treatment or surgery at any time and parental smoking was given to patient's parents.

A physical examination was performed in all children by the same investigator. Each patient's growth was assessed and compared with the standard growth curve of Swiss children.

After the clinical examination, the patient underwent pulmonary function testing in the following order: nitric oxide measurement, spirometry and body plethysmography, measurement of airway impedance using a forced oscillation technique and finally a methacholine bronchial provocation test.

Exhaled nitric oxide

Exhaled nitric oxide was measured on-line using the single-breath technique by means of a chemiluminescence analyser (CLD 88 EXHALYZER, ECO MEDICS AG, Switzerland). Measurements were made according to European Respiratory Society (ERS) guidelines.

Lung function

Spirometry and whole body plethysmography were performed according to standardised criteria using the measurement unit MasterLabPro (Jaeger GmbH, Würzburg, Germany).

The following parameters were recorded: forced vital capacity (FVC), forced expiratory volume in first second (FEV_1), peak expiratory flow (PEF), FEV_1/FVC ratio, maximum expiratory flow at 75%, 50% and at 25% FVC (MEF_{75}, MEF_{50}, MEF_{25}) and MEF_{75-25} ratio. The reference values from Zapletal et al. [9] were used for analysis.

Whole body plethysmography was performed in the same laboratory (MasterLabPro, Jaeger, Würzburg, Germany). The following parameters were recorded:

Total lung capacity (TLC), residual volume (RV), vital capacity (VC), intra-thoracic gas volume (ITGV), total resistance (R tot), total specific airway resistance (SR tot), RV%/TLC ratio, and ITGV%/TLC ratio.

Bronchial hyper-responsiveness

The bronchial provocation test with methacholine (MCH) was performed, when the baseline FEV_1/VC ratio was at least 0.7. MCH was given in doubling concentration of 0.01 mg/ml to 2 mg/ml using a calibrated nebulizer and FEV_1 was measured after each dose-step until the FEV_1 value had fallen from baseline by at least 20%.

Forced oscillation

The impedance of the total respiratory system was measured using an oscillometry system (Quark i2m Forced Oscillation Measurement system, Chess medical technology, NV). Three reproducible measurements were selected for the analysis in order to calculate a mean value for the resistance of the respiratory system at 8 Hz (Rrs 8), which is considered to be highly associated with bronchial obstruction. The results were compared to the reference values supplied by manufacturer [10].

Statistical analysis

Results are expressed as mean (SD) for continuous data or median with range. Continuous data from CDH survivors and non-survivors as well as questionnaire data taken at follow-up visit were tabulated and described as numbers. Lung function data were described as percent predicted. The relationship of the most important data is shown using scatter plots, the corresponding coefficient of correlation is also given.

Results

Patient presentation and initial management

During the ten-year period, 46 patients with CDH were admitted to the University Children's Hospital Zurich. Demographic data of all patients are shown in table 1.

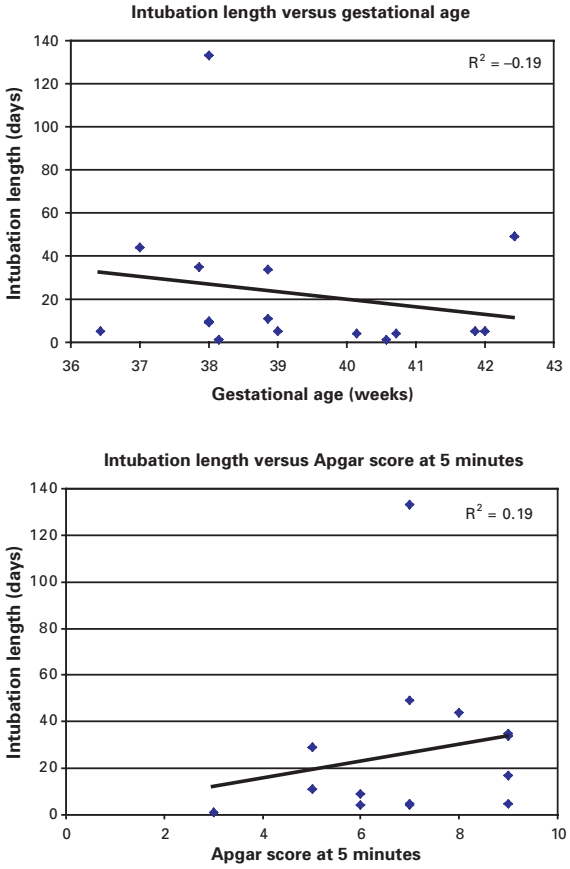


Figure 1

Intubation length versus gestational age and Apgar score at 5 minutes.

Thirty (65%) children survived to discharge from the hospital. Median age at surgery was 4 days [2 and 21 days]. In the group of survivors, 17/30 (57%) children were operated within 96 hours of presentation. The median for duration of artificial ventilation in the group of survivors was 12 days [1 and 162 days]. Neither gestational age nor Apgar score at five minutes correlated with intubation length (fig. 1).

Follow-up

From the 30 survivors, eleven children were either lost to follow-up or refused consent to the study. The remaining 19 (63%) were recruited to attend the long-term follow-up. Mean (SD) age at follow-up was 8.2 (2.8) years. The patient characteristics of survivors, those who died and the children included in the follow-up study are presented in table 1.

Questionnaire

A review of questionnaires revealed that respiratory problems occurred most commonly in the first three years of life. At least one wheezy episode requiring bronchodilators was present in 8/19 (42%) children during this period. Recurrent wheezing episodes (3/year) in the first three years of life were reported by parents of 4/19 (21%) children. The duration of artificial ventilation, ICU-hospitalisation length and total hospitalisation length did not correlate with recurrent respiratory symptoms later in childhood. In two children the diagnosis of allergic bronchial asthma was established. Smoking occurred in 6/19 (30%) of the households. 5 of 6 CDH patients postnatally exposed to tobacco smoke were using bronchodilators in the year previous to follow-up ($r^2 = 0.49$).

Table 1

Patient characteristics and initial management according to outcome and to participation in the study. Continuous variables are summarised by either the mean (SD) or the median [range].

	Died	CDH survivors as a whole group	CDH survivors participated in the study	CDH survivors lost from follow-up
Number	16 (11 male)	30 (16 male)	19 (11 male)	11 (5 male)
Gestational age, weeks	38 [33, 42]	38 [30, 42]	38 [30, 42]	39 [33, 41]
Birth weight, g	3100 [1700, 4250]	3000 [2250, 3900]	3000 [2400, 3900]	3000 [2250, 3900]
5 minute Apgar score	6 (2)	7 (1)	7 (1)	6 (1)
Side of CDH				
Right	2	2	1	1
Left	16	30	19	11
Day of surgery	*	5 [2, 21]	5 [2, 21]	5 [2, 17]
Duration of artificial ventilation, days	3 [1, 195]	12 [2, 120]	7 [2, 33]	15 [2, 120]
Length of ICU Hospitalisation, days	3 [1, 195] †	16 [2, 133]	13 [2, 133]	18 [4, 128]
Total Hospitalisation Length, days	3 [1, 195] †	30 [10, 156]	30 [12, 145]	30 [10, 156]

* 13/16 of non-surviving CDH patients succumbed to respiratory failure before a surgical intervention could be performed.
† all patients died on ICU.

The family history (first degree) for an atopic disease was positive in 8/19 (42%) cases.

GER requiring pharmacological treatment was present in 3/19 (16%) children and one child underwent Nissen fundoplication. The questionnaire data are summarised in table 2.

Clinical examination

Mild to moderate developmental delay was present in two children. These patients were not able to perform the lung function tests reliably.

Height values were within normal range in all children, and only two children presented with a body weight below the 3rd percentile.

Lung function

16 children performed a reproducible and acceptable forced vital capacity manoeuvre, whereas acceptable whole body plethysmography tests were obtained in only 11 children, aged 6 to 13 years.

As a whole group, the CDH patients showed a mild reduction in the majority of measured parameters compared to predicted values (table 3).

The individual analysis of measured parameters showed normal values in only 7/16 (44%) subjects. Four children had restrictive pulmonary disease; four had evidence of airflow limitation and one child showed a mixed pattern of pulmonary disease.

Correlation between lung function results and patient characteristics

The spirometric parameters (FVC, FEV_1, FEV_1/FVC, MEF_{75}, MEF_{50}, MEF_{25} and MEF_{75-25}), did not correlate with either gestational age, birth weight or 5 minute Apgar score (for example, fig. 2).

Neither duration of assisted ventilation nor the ICU hospitalisation length and total hospitalisation length showed any significant correlation with spirometric parameters (fig. 3).

Similar figures, i.e. no significant correlations, were found for plethysmographic parameters.

Positive familial history of atopy or asthma and tobacco smoke exposition did not significantly affect the measured lung function parameters.

Measurement of exhaled nitric oxide (eNO)

Mean value of eNO for the whole group was 11 (12) ppb. The highest eNO value, 58 ppb, was obtained in a child with bronchial asthma and allergy.

The remaining patients had eNO levels between 2 and 15.2 ppb, which was considered

Table 2

Data from questionnaire regarding the respiratory problems and gastro-esophageal reflux as reported by parents of the CDH survivors (N = 19) at follow-up visit.

	N	%
Family history of atopy	9	47
Family history of asthma	5	26
Current asthma	2	10
At least 1 episode of obstructive breathing	9	47
Recurrent wheezing or persisted cough	4	21
Tobacco smoke exposition	6	32
Smoking (mother) during pregnancy	1	5
Past history of GER* in early childhood	4	21
Fundoplication	1	5
GER symptoms in last 12 months	1	5
Bronchodilator therapy in last 12 months	9	47

* Gastroesophageal reflux requiring pharmacological or surgical therapy.

Table 3

Pulmonary Function Testing at follow-up visit.

Body plethysmography (N = 11)	
Total Lung Capacity (TLC)	93 (20)
Vital Capacity	75 (18)
Intrathoracic Gas Volume (ITGV)	107 (23)
Residual Volume (RV)	131 (67)
RV/TLC	136 (63)
ITGV/TLC	110 (41)
Resistance total	175 (47)
Specific Resistance total	227 (102)
Spirometry (N = 16)	
Forced Vital Capacity (FVC)	67 (19)
Forced Expiratory Volume in 1st second (FEV_1)	74 (21)
FEV_1/FVC	109 (8)
Peak Expiratory Flow	67 (24)
Mean Expiratory Flow at 75% of Vital Capacity (MEF_{75})	66 (27)
Mean Expiratory Flow at 50% of Vital Capacity (MEF_{50})	68 (34)
Mean Expiratory Flow at 25% of Vital Capacity (MEF_{25})	69 (48)
MEF_{75-25}	68 (37)

Values shown are means of percent-predicted (SD) except for RV/TLC, ITGV/TLC and FEV_1/FVC, which are defined as percent.

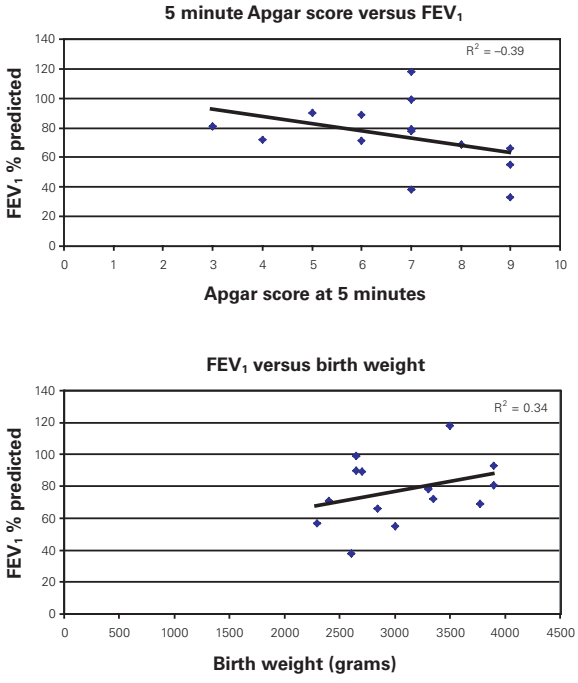
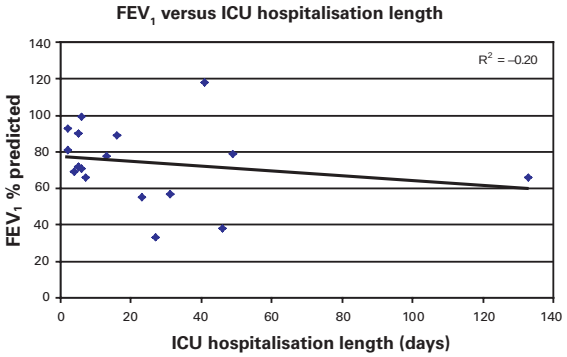


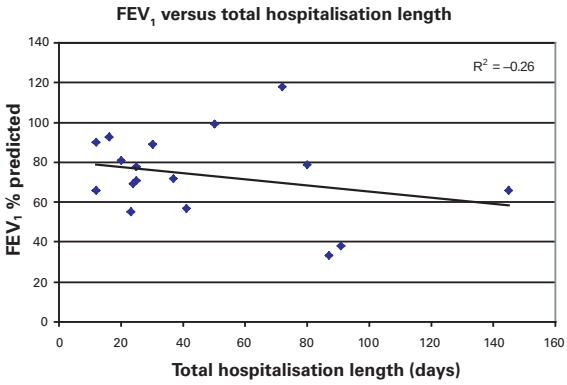
Figure 2

FEV_1 versus Apgar score at 5 minutes and birth weight.

Figure 3

FEV_1 versus ICU hospitalisation length and total hospitalisation length.





within normal limits. No significant correlation was found between eNO on the one hand and a family history of asthma or allergy, tobacco smoke exposition, history of GER or recurrent wheezing episodes in the first year of live on the other hand. Similarly, the duration of assisted ventilation and total hospitalisation time did not correlate with eNO (fig. 4).

Methacholine bronchial provocation test

Only eight patients correctly completed the bronchial challenge test. Inhalation of methacholine resulted in a 20% or more decrease of FEV_1 in 6/8 (75%) children.

All the patients with positive methacholine bronchial provocation test had eNO values between 1.8 and 11.1 ppb.

Measurement of resistance using the forced oscillation technique

15 children successfully performed the FOT measurement. 9/15 (60%) children showed increased resistance measured at 8 Hz (Rrs 8). The duration of artificial ventilation, ICU hospitalisation time and total hospitalisation time did not correlate with the Rrs 8 (fig. 5).

Similarly, no significant correlation was found for Rrs 8 and family history of allergy or asthma, recurrent respiratory symptoms or eNO. Six children with increased Rrs 8 also had abnormal lung function in spirometry. Two other children with increased Rrs 8 but normal spirometry had already been exposed to tobacco smoke prenatally and had received bronchodilator therapy in the year prior to the follow-up visit. We found no correlation between oscillatory resistance and the specific airway resistance measured by whole body plethysmography.

Discussion

The overall mortality rate of 35% in our study is similar to that reported from other tertiary care paediatric centre-based studies [11]. It is well known that some live-born infants with CDH die before referral to a tertiary centre. Consequently, the population of infants reaching a tertiary care centre commonly represents only 40–50% of the total number of cases of CDH. This disparity reflects the "hidden mortality" of CDH as first described by Harrison et al. [12]. Due to a well-developed prenatal screening programme in Switzerland it can be assumed that the overall mortality of CDH patients calculated on behalf of a population-based study would be twice as high [13].

The limited number of patients (63% of all survivors) who underwent follow-up assessment is a potential weakness of the study. As shown in table 1, there was only a minimal difference in most of the descriptive parameters of CDH survivors who participated in the study and those who were lost to follow-up. Recent studies have shown that gastroesophageal reflux is commonly found in survivors of CDH [14]. The reported incidence of GER depends partially on the diagnostic methods used. Using a questionnaire we found symptoms consistent with GER requiring pharmacological or surgical therapy beyond the neonatal period in four patients. Recurrent bronchitis, aspiration pneumonia and worsening pulmonary function were reported as respiratory complications of GER. Anti-reflux surgery is reserved for pathologic GER that persists despite maximisation of medical therapy. In our study group, only one patient required a Nissen fundoplication. Failure to thrive is frequently described in CDH survivors. The relative low incidence of GER and of severe pulmonary impairment could explain the low incidence of failure to thrive in our group of patients.

Many studies report a high incidence (>60%) of chronic lung disease initially [15, 16] with improvement in most children with CDH repair during the first few years of life. The same trend was noted in our study. 8/19 (42%) of the children followed up presented with wheezy episodes early in life. Respiratory symptoms became less common and milder as patients grew older, nevertheless 8/19 (42%) patients had received bronchodilator therapy in the year prior to the follow-up. 2/19 (10%) children were diagnosed as having bronchial asthma. This corresponds well with the

Figure 4

Exhaled nitric oxide (eNO) versus intubation length and total hospitalisation length.

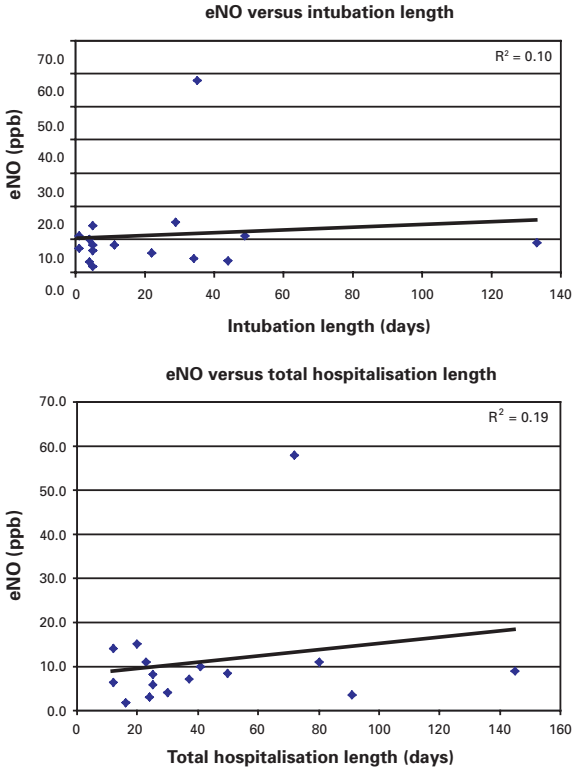
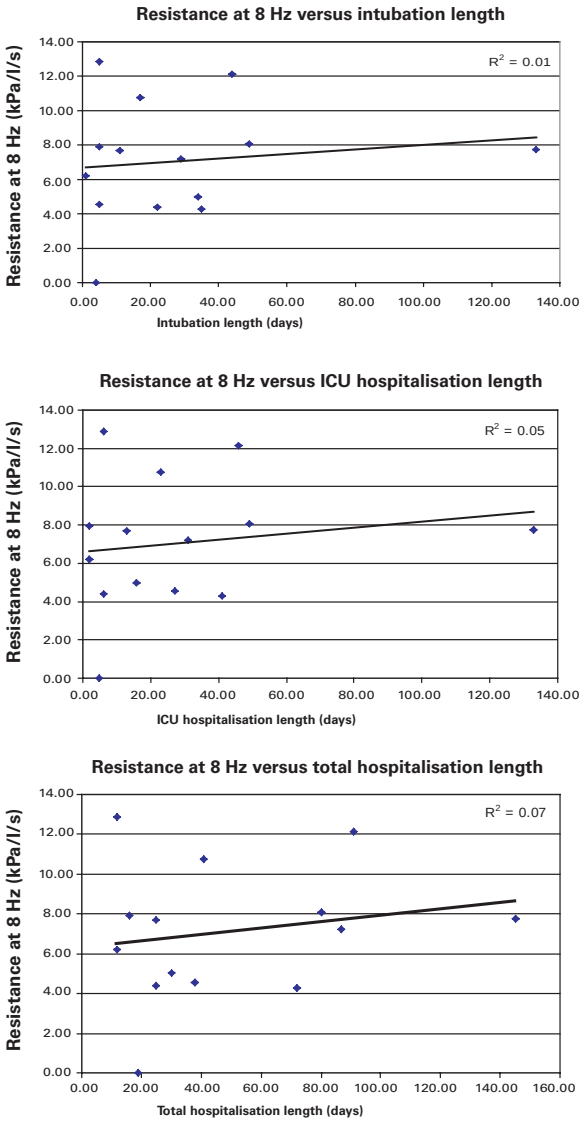


Figure 5

Resistance at 8 Hz (R8) versus intubation length, ICU hospitalisation length and total hospitalisation length.



overall incidence of childhood asthma in Switzerland (8%).

The follow-up group of CDH patients in our study represented 63% of all survivors. It is a not unknown phenomenon that parents of more severely ill children are more likely to refuse to participate in studies than those of less severely affected children. As shown in table 1, the CDH survivors who were lost to follow-up had a slightly prolonged duration of artificial ventilation and prolonged hospitalisation time. It is possible that had these patients been included in the analysis we would have seen a higher incidence of respiratory problems.

In the last years, several studies looking at lung function outcomes in children surviving congenital diaphragmatic hernia have been performed [17, 18]. In the present series, we found various degrees of obstructive or restrictive ventilatory impairment in 50% of the patients, a figure comparable with results from other studies [19, 20]. We typically observed lowering of functional lung volumes with a tendency to hyperinflation. Interstitial emphysema [21], increased airway collapsibility and decreased compliance of chest wall or diaphragm may be responsible for these functional changes.

In our study sample, lung function parameters were not predicted by perinatal factors. Contrary to other, larger studies [20] we found no significant correlation for lung function parameters and duration of artificial ventilation. The only weak trend showing increasing lung function impairment, i.e. smaller FEV_1, depending on the length of intubation, could be the result of the small sample size in our study.

We are aware that there is a significant limitation due to the small number of patients who correctly performed the methacholine provocation test in our study. In consequence, we do not attempt to draw any conclusion on the basis of this data and we present the data in a descriptive way only.

This is the first follow-up study in CDH to include a measurement of respiratory system resistance using a forced oscillation technique. Our aim was to assess the ability of the forced oscillation technique to detect the alterations in the respiratory mechanics in CDH patients. There are many studies addressing respiratory mechanics in lung disease in childhood [22, 23] suggesting that FOT detects abnormal airway resistance more peripherally in the lung and hence may give more information about the peripheral airways as compared to spirometry. The fact that 9/15 (60%) of CDH patients had an increased resistance measured at 8 Hz and that six of these children also had an abnormal spirometry pattern may suggest symmetrical involvement of both small and large airways. This type of abnormal lung mechanics could be explained by lung and bronchial tree hypoplasia.

There are no data on exhaled nitric oxide (eNO) at long-term follow-up in children with CDH. Epithelial cells of the bronchi have been identified as the main source of exhaled nitric oxide

and abnormal values for eNO have been reported in many respiratory conditions. Patients with bronchopulmonary dysplasia (BPD) have been studied in regard to exhaled nitric oxide (eNO). Baraldi et al. [24] found eNO values in school-age survivors of BPD to be four times lower compared with a group of patients with asthma with a comparable airflow limitation. Others have found normal values for eNO in non-atopic schoolchildren with a history of BPD [25]. The duration of artificial ventilation and oxygen therapy in CDH patients is in many cases comparable to that in BPD patients and dysplasia of the bronchial tree has often been described in CDH survivors. Hence, CDH survivors represent a group of patients with potentially abnormal airway nitric oxide production.

Analysed as a whole group, we found normal values for exhaled nitric oxide. Exhaled NO is presently recognised as a marker of airway inflammation and is related to bronchial hyper-responsiveness in asthmatic patients [26]. Therefore, one may hypothesize that reasons other than airway inflammation are responsible for the bronchial hyper-responsiveness seen in many of the CDH survivors. The reduced spirometry parameters in context with normal eNO values seen in our group of CDH survivors may indicate that the lung function impairment has a structural rather than an inflammatory origin.

In conclusion, the results of follow-up assessments presented are in agreement with other published studies and demonstrate a good general prognosis for surviving CDH patients. Children who survived CDH repair have reduced functional lung volumes but normal TLC. Exhaled nitric oxide in non-atopic CDH survivors is normal. FOT can be used as a screening method to detect CDH survivors with abnormal spirometry parameters. Even in the absence of clear clinical significance, the incomplete functional recovery of the lung in CDH survivors and the risk of neurodevelopmental and nutritional morbidity require long-term follow-up in a paediatric centre. This follow-up should include a multidisciplinary team consisting of paediatric surgeons, neonatologists, paediatric pulmonologists, paediatric orthopaedic specialists, gastroenterologists, dieticians and cardiologists.

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