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PULMONARY FUNCTION AND EXERCISE CAPACITY IN SURVIVORS OF CONGENITAL DIAPHRAGMATIC HERNIA

- Running title: Cardiopulmonary function in children with CDH

Marieke G Peetsold (1), Hugo A Heij (2), Ad F Nagelkerke (1), Hanneke IJsselstijn (3), Dick Tibboel (3), Philip H Quanjer (4), Reinoud JBJ Gemke (1)

(1) VU University Medical Centre, Amsterdam, The Netherlands, Department of Pediatrics
(2) Pediatric Surgical Centre of Amsterdam (VU University Medical Centre/Emma Children's Hospital/AMC), The Netherlands
(3) Erasmus Medical Centre/Sophia Children's Hospital, Rotterdam, The Netherlands, Department of Pediatric Surgery
(4) Erasmus Medical Centre/Sophia Children's Hospital, Rotterdam, The Netherlands, Department of Pediatrics

Correspondence to:

M.G. Peetsold, MD

Department of Pediatrics, VU University Medical Centre

PO Box 7057

1007 MB Amsterdam

The Netherlands

Tel + 31-20-4443319

Fax + 31-20-4442918

m.peetsold@vumc.nl

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ABSTRACT

Introduction

Congenital diaphragmatic hernia (CDH) is associated with pulmonary hypoplasia and pulmonary hypertension. The objective of this study was to assess pulmonary function and exercise capacity and its early determinants in children and adolescents born with high-risk CDH (CDH associated respiratory distress within the first 24 hours) and to explore the relation of these findings with CDH severity.

Methods

Of 159 patients born with CDH, 84 survived. Of the 69 eligible patients, 53 children (mean age 11.9 ± 3.5 years) underwent spirometry, lung volume measurements and maximal Cardiopulmonary Exercise Testing (CPET). Results of the pulmonary function tests were compared to those from a healthy control group matched for gender, age and height.

Results

CDH survivors have a significantly lower FEV_1, FVC, FEV_1/FVC, MMEF and PEF when compared to healthy controls. RV/TLC ratio was significantly higher. Linear regression analysis showed that gastro-esophageal reflux disease was an independent determinant of reduced FEV_1 and FVC. CPET results were normal in those tested.

Conclusion

High risk CDH survivors have mild to moderate pulmonary function abnormalities when compared to a healthy matched control group, which may be related to gastro-esophageal reflux disease in early life. Exercise capacity and gas exchange parameters were normal in those tested, indicating that the majority of patients do not have physical impairment.

INTRODUCTION

Congenital diaphragmatic hernia (CDH) is a life-threatening anomaly with a mortality rate ranging from 10-50%, depending on case selection.[1-3] Pulmonary hypoplasia, pulmonary hypertension and CDH associated malformations are major determinants of morbidity and mortality.[4] CDH is accompanied by a variable degree of hypoplasia of the ipsilateral and contralateral lung, characterized by a reduction of the number of airways, alveoli and vascular generations.[5;6] Respiratory failure requiring ventilatory support immediately after birth is a characteristic of high risk CDH. Many patients require high pressures and high fractions of inspiratory oxygen to provide adequate oxygenation, which may lead to further pulmonary damage.[4;7;8] Since the asymmetry of the lungs, due to pulmonary hypoplasia, results in areas of different compliance and therefore potential hyperinflation and overexpansion of alveoli, risk of barotrauma in CDH patients may even increase further.[9] CDH is also associated with pulmonary hypertension, which may be the result of failure of normal structural remodeling of the pressure-regulating pulmonary arteries after birth, as described in deceased CDH patients.[10;11] Scintigraphic studies have demonstrated that in CDH survivors, mean perfusion of the ipsilateral lung was lower when compared to healthy children.[12-15] and when compared to the contralateral lung [12;13] suggesting residual vascular abnormalities.

To improve the understanding of the long-term consequences of pulmonary hypoplasia and pulmonary vascular abnormalities, the primary objective of this study was to assess pulmonary function and exercise capacity in a group of patients aged 6-18 years, who had undergone surgical repair of high risk congenital diaphragmatic hernia in the neonatal period. Results of the pulmonary function tests were compared to a matched control group. The secondary objective was to explore early (particularly CDH related) determinants of pulmonary function and/or exercise-tolerance in later life.

MATERIAL AND METHODS

Patients

All patients born with high risk CDH referred to the Pediatric Surgical Center of Amsterdam between 1987 and 1999, and to the Sophia Children's Hospital in Rotterdam between 1988 and 1994, were eligible for this study. Children who were treated at the Sophia Children's Hospital after 1994 or treated with ECMO (since 1991) were included in another follow-up program and were therefore not approached. Patients were included if they developed CDH associated respiratory distress within the first day of life (high risk CDH). Patients were excluded if they had other serious anomalies or were incapable of adequately performing all tests.
Permission for the study was granted by the Institutional Review Board. Written informed consent was obtained from all patients and their parents or guardians prior to inclusion.
Patients' charts were reviewed, focusing on relevant perinatal and postnatal variables.

Study design

Patients who gave informed consent attended the out-patient clinic for a study visit. Pulmonary function testing included spirometry and lung volume measurements were followed by Cardiopulmonary Exercise Test (CPET). For the pulmonary function test, patients were matched for height, age and gender with schoolchildren and adolescents that have been studied independently in the past. The studies of Dutch schoolchildren [16] and that of adolescents [17] have been described in detail previously. Schoolchildren were studied, with informed consent from the parents, between 1984 and 1986, and adolescents between 1978 and 1984. All matched controls were healthy and lifelong non-smokers.

Pulmonary function tests

Patients performed standard spirometry and underwent lung volume measurements according to the guidelines of the ECCS/ERS.[18] All medication was discontinued 24 hours prior to testing. Forced expiratory volume (FEV_1), forced vital capacity (FVC), maximum midexpiratory flow (MMEF) and peak expiratory flow (PEF) were determined from the largest of three reproducible manoeuvres using a mass flow sensor (Vmax 229, Sensor Medics, Yorba Linda, CA, USA).[18] Spirometry was repeated after inhalation of 4x100 µg salbutamol dose-aerosol to evaluate the reversibility of potential bronchial obstruction and in order to prevent exercise-induced bronchoconstriction. A change in $FEV_1 \geq 12\%$, expressed as percentage of the predicted value, was considered a significant response.[18]

Lung volume measurements were carried out after bronchodilation. Vital capacity (VC), total lung capacity (TLC) and residual volume (RV) were determined by the multibreath nitrogen washout method [19]. The mean of three reproducible manoeuvres was used for analysis.

Results were expressed as z-scores calculated as the difference between observed and predicted value divided by the residual standard deviation from the reference values.[20] Since Stanojevic *et al.* did not provide reference values for the PEF, these results were expressed as L/s. The RV/TLC ratio was expressed as a percentage. Z-scores < -1.64 (5^{th} percentile of the reference population) were considered abnormally low.

In the matched controls all measurements were obtained without bronchodilation. Flow-volume curves were obtained by dry rolling-seal spirometer in children, and with a Fleisch III pneumotachometer in adolescents. In adolescents, but not in schoolchildren, residual volume was obtained by the forced nitrogen rebreathing technique described and validated by Sterk *et al*. [21]. The longitudinal data of growing children [16] were used to construct a cross-section by selecting at random one record from a person's available measurements so that the new data set had an age distribution that was as uniform as possible, each person being represented only once. Thus data were available on 123 girls and 361 boys. Regressions equations were derived that gave the best fit to the data (table 1).

Table 1. Regression equations derived from the data of growing children [16], which were used to calculate the z-scores for the lung volume measurements. Height is expressed in cm and age in years.

ln: natural logarithm; RSD: residual standard deviation; RV: residual volume; TLC: total lung capacity.

Index	Equation	R^2	RSD
		Girls	
ln RV	2.61 * ln(height) + 0.056 * age – 2.11	0.447	0.235
ln TLC	2.567 * ln(height) + 0.030 * age – 0.168	0.692	0.109
RV/TLC (%)	13.157 + 0.589 * age	0.079	4.20
		Boys	
ln RV	2.738 * ln(height) + 0.067 * age -2.375	0.616	0.239
ln TLC	2.698 * ln(height) – 0.041 * age – 0.412	0.866	0.101
RV/TLC (%)	12.816 + 0.580 * age	0.063	4.27

Cardiopulmonary exercise testing

Maximal exercise capacity was assessed using the Bruce treadmill test. The Bruce test protocol calls for three minute stages of increasing belt speed and per cent grade on a treadmill (Marquette, 2000 treadmill).[22] Children were always tested in the presence of their parent(s). Each patient was allowed to familiarize with the mouth piece and the treadmill during a 3 minute period prior to the start of the test. Each child was urged to continue to the point of severe fatigue. Heart rate and oxygen saturation were monitored by finger pulse oximetry.

The parameters measured during the CPET were minute ventilation ($\dot{V}E$), oxygen uptake ($\dot{V}O_{2,max}$), oxygen pulse (O_2-pulse; *i.e.* oxygen uptake divided by the heart rate), respiratory exchange ratio (RER), ratio of ventilation to CO_2 output ($\dot{V}E,CO_2$), the respiratory rate and the duration of the exercise test. Respiratory gases were monitored on a breath-by-breath basis using a flow sensor (Vmax 229, SensorMedics, Yorba Linda, CA, USA).

The CPET was considered adequate if one or more of the following conditions were achieved: at least 80% of the maximum predicted heart rate (determined as 220 minus age), RER >1.0 during one minute or exhaustion of the subject.[23]

The $\dot{V}O_{2,}max$ and the $\dot{V}O_{2,}max/kg$ were expressed as z-scores calculated from reference values.[24] Z-scores < -1.96 (2.5^{th} percentile of the reference population) were considered abnormally low.

Statistical analysis

Statistical analysis was performed using the unpaired t-test or the one-sample t-test with 0 as reference for normally distributed continuous data. The Kolmogorov-Smirnov test was used to determine whether results were normally distributed. Non-parametric tests were used for non-normally distributed continuous data. The Fisher exact test or the Chi-square test were used for comparing categorical data.To explore the relation between early (perinatal and neonatal) risk factors and lung function in later life, linear regression analysis with pulmonary function parameters and CPET results as dependent variables was performed. Statistical significance was defined as $p < 0.05$. SPSS 15.0 was used for data analysis.

RESULTS

Patient characteristics

One hundred and eighty two patients born with CDH were referred to the Pediatric Surgical Center of Amsterdam between 1987 and 1999, and the Sophia Children's Hospital between 1988 and 1994, 84 of them survived. Fifteen patients were excluded because of treatment with ECMO (seven patients), mental retardation (three patients), trisomy 21 (two patients), pentalogy of Cantrell (one patient), pulmonary hemosiderosis (one patient) and missing patient file (one patient).

Of the 69 high-risk CDH patients eligible for this study 53 (77%) agreed to participate (figure 1). Thirty-three patients were treated in the Pediatric Surgical Centre of Amsterdam and 20 in the Sophia's Children Hospital. A comparison of the 53 participating patients with those who were unwilling to participate disclosed no significant differences (table 2).

Table 2.

Characteristics of participating and non-participating patients did not differ significantly. Numbers indicate numbers of patients, except birth weight, gestational age and ventilation. These variables are expressed as mean ± SD unless otherwise stated.

* GERD was demonstrated by gastrointestinal X-ray series, pH-metry and/or endoscopy in the first 2 years after CDH repair.

AS: Apgar score; CDH: congenital diaphragmatic hernia; GERD: gastro-esophageal reflux disease

	Participating (n = 53)	**Not participating (n = 16)**	**p-value**
Male	29 (55%)	9 (56%)	1.00
Birth weight (grams)	3198 ± 670	3076 ± 450	0.52
Gestational age (weeks)	38.9 ± 2.2	39.4 ± 1.7	0.75
AS 5 minute ≤ 5	8 (15%)	2 (13%)	1.00
Symptoms ≤ 6 hrs after birth	45 (85%)	13 (81%)	1.00
Left sided CDH	45 (85%)	16 (100%)	0.22
Ventilation median days (range)	8.0 (1-66)	13.0 (0-36)	0.61
Patch reconstruction	19 (36%)	7 (44%)	0.63
Astma in history	15 (28%)	3 (19%)	0.53
GERD in history*	19 (36%)	8 (50%)	0.40
Cardiac abnormalities	8 (15%)	5 (31%)	0.15
Recurrent CDH	5 (9%)	1 (6%)	1.00

Four children were born before a gestational age of 36 weeks (minimum 31 weeks). CDH repair was performed 2.8 ± 3.7 days (mean ± SD, median 2 days, range 0-23 days) after birth. CDH repair was only performed when patients were stabilized and adequately oxygenated. Lung protective ventilation strategies were used in both neonatal care units. Median hospital stay was 24 days (range 10-330 days).

Neurological abnormalities were reported in 13 patients (25%), 11 patients had a developmental delay and two patients had muscle tone abnormalities.

Persistent pulmonary hypertension of the neonate (PPHN) was well documented in only seven cases (13%), while in many files accurate information was missing. One patient was discharged with oxygen, which was continued for three months after discharge.

Mean age (SD) at follow-up was 11.9 (3.5) years (range 6 – 18 years). None of the patients used antireflux medication at the time of follow-up.

Pulmonary function

One patient was extremely anxious and therefore refused to perform the pulmonary function test. Spirometry and lung volume measurements of four patients (8%) could not be reproduced and were excluded from analysis. In 10 children (19%) bronchodilator responsiveness was not tested because of technical difficulties.

Z-scores of all pulmonary function test results were normally distributed. The FEV_1 z-score before bronchodilation (BD) was abnormally low (< -1.64) in 22 CDH patients (46%) *vs* 0 in the control group ($p < 0.001$); in twelve CDH patients there was a >12% increase in FEV_1 after bronchodilation (five not tested). In 12 out of 48 CDH patients (25%) the FEV_1/FVC z-score was abnormally low (< -1.64) before BD *vs* 3 subjects (6%) in the control group ($p = 0.007$). Mean FEV1, FVC, FEV1/FVC, MMEF and PEF were significantly lower in CDH patients when compared to the control group (table 3).

The RV/TLC ratio exceeded +1.64 SD in 25 patients (52%) vs 0 in the control group ($p < 0.001$), in 19 (76%) this was due to an elevated RV, in 5 (20%) to a decreased TLC, and in 1 patient (4%) to a combination.

Restrictive impairment (TLC z-score < -1.64 SD) was demonstrated in 8 patients (17%) vs 0 in the control group ($p = 0.02$).

Table 3. Results of the spirometry and lung volume measurements of the CDH patients. Results are expressed as z-scores calculated from a reference population [20], except the PEF that is expressed as L/sec and the RV/TLC ratio that is expressed as percentage.

95% CI: 95% confidence interval; BD : bronchodilation; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; MMEF: maximum mid-expiratory flow; PEF: peak expiratory flow; TLC: total lung capacity; RV: residual volume; SD: standard deviation.

	Before BD

Spirometry	CDH n =48		Controls n = 48		p-value	95% CI of the difference Upper limit	Lower limit
	(mean ± SD)	Range	(mean ± SD)	Range			
FEV_1	-1.63 ± 1.78	-7.14 – 1.45	0.08 ± 0.90	-1.53 – 2.38	< 0.001	-2.28	-1.14
FVC	-1.28 ± 1.62	-6.33 – 1.93	0.05 ± 0.87	-1.57 – 2.76	< 0.001	-1.85	-0.80
FEV_1/FVC	-0.84 ± 1.27	-4.03 – 1.07	0.05 ± 0.90	-2.04 – 1.90	< 0.001	-1.33	-0.44
MMEF	-1.57 ± 1.70	-6.18 – 1.08	0.16 ± 1.03	-2.31 – 2.27	< 0.001	-2.30	-1.16
PEF (l/sec)	4.89 ± 1.79	1.42 – 8.23	6.45 ± 2.10	3.16 – 10.34	< 0.001	-2.34	-0.78
	After BD						
Spirometry	**CDH n = 38**		**Controls**		**p-value**	**95% CI of the difference Upper limit**	**Lower limit**
	(mean ± SD)	**Range**	**(mean ± SD)**	**Range**			
FEV_1	-1.45 ± 1.51	-6.22 – 1.43					
FVC	-1.45 ± 1.46	-5.67 – 2.05					
FEV_1/FVC	-0.22 ± 1.30	-2.83 – 1.77					
MMEF	-0.22 ± 1.30	-5.54 – 2.19					
PEF (L/sec)	5.38 ± 1.80	2.36 – 9.02					
Lung volumes	**n = 48**		**n = 29**				
TLC	0.16 ± 1.91	-4.16 – 1.55	0.03 ± 1.04	-1.86 – 1.93	0.70	-0.54	0.80
RV	0.98 ± 2.06	-5.37 – 2.44	-0.24 ±0.84	-2.17 – 0.98	0.001	0.55	1.89
RV/TLC (%)	26.7 ± 9.0	6 - 47	20.4 ± 3.0	14 - 25	<0.001	3.50	9.13

Linear regression analysis disclosed a negative association between GERD and both FEV_1 and FVC before BD (table 4). Patients who were ventilated at least 7 days had a significantly lower FEV_1 z-score after BD and FVC before BD (figure 2A). Patients who had undergone antireflux surgery had significantly lower z-scores for FEV_1, FVC, MMEF and TLC (figure 2B). There was a trend towards higher age at follow-up and lower z-scores for FEV_1 ($p = 0.051$) and FEV_1/FVC ($p = 0.06$) in CDH patients (figure 3A, B and C respectively). There was no association between age and the z-score for FVC ($p = 0.22$)

Table 4. Stepwise multivariate regression models for several pulmonary function parameters (expressed as z-scores, unless otherwise stated). Independent variables were duration of ventilation, early GERD (<2 yrs after CDH correction), side of defect, asthma in 1st grade family members, atopy and parental smoking.
BD : bronchodilation; GERD: gastro-esophageal reflux disease; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; RV: residual volume; SE: standard error; TLC: total lung capacity.

	B	SE	p	Adjusted R^2
FEV_1 before BD				
Early GERD	-1.29	0.385	0.002	0.19
constant	-0.73	0.243		
FVC before BD				
Early GERD	-1.536	0.438	0.001	0.10
constant	-0.932.	0.277		
FVC after BD				
Duration of ventilation	-0.026	0.011	0.03	0.12
constant	-1.018	0.252		
RV/TLC (%)				
Duration of ventilation	0.179	0.081	0.03	0.08
constant	24.13	1.684		

Maximum exercise testing

Eight patients did not perform a cardiopulmonary exercise test (CPET) for the following reasons: refusal (five patients), technical problems (two patients) and one patient skipped CPET because a severely impaired pulmonary function (FEV_1 z-score -7.14). Pulmonary function results were significantly lower for patients who

did not perform the CPET (FEV_1 z-score –3.93 vs –1.10; p = 0.002 and FEV_1/FVC z-score –2.49 vs -0.76; p = 0.02).

Forty-five patients underwent CPET. Results of nine patients were excluded from analysis because they did not reach the level of maximal exercise due to painful legs (6 patients), mild motor skills disorder (one patient), shortness of breath (one patient) and being too small to fulfil the protocol (one patient). Six of them had a history of developmental delay, which might have influenced exercise performance. Pulmonary function results of the patients who did not achieve maximal exercise were similar to those who did. Four children had mild transcutaneous desaturation (Stc,O_2 84-94%) during CPET, 2 of them did not achieve maximal exercise due to painful legs.

Reliable exercise data could be obtained in 36 children and showed that three children had an abnormally low $\dot{V}O_{2,max}$ z-score (< -1.96). In one child this was accompanied by a reduced peak O_2 pulse (O_2-pulse ≤ 80% predicted), whereas two patients had airway obstruction (FEV_1/FVC z-score –2.80 and –2.00). Overall the mean $\dot{V}O_{2,max}$ z-score did not differ significantly from normal values (-0.23 ± 1.58; mean ± SD; p = 0.39) (table 5).

Table 5. Results of the cardiopulmonary exercise testing. Numbers are expressed as mean ± SD.

$\dot{V}E$: minute ventilation; FEV_1: forced expiratory volume in one second; SD: standard deviation; Stc,O_2: transcutaneous oxygen saturation; $\dot{V}E,CO_2$:ratio of ventilation to CO_2 output.

Parameter		95% CI	
	Mean ± SD	**Lower bound**	**Upper bound**
Heart rate max (% predicted)	97.7 ± 1.3	96.4	99.4
Respiratory rate max (x/min)	57.9 ± 14.4	53.0	62.9
Respiratory exhange ratio	1.09 ± 0.13	1.05	1.13
$\dot{V}_E$ max (L/min)	71.4 ± 26.8	62.3	80.4
O_2 pulse (% predicted)	102.7 ± 17.1	96.4	108.9
$\dot{V}O_{2,}$max (z-score)	-0.23 ± 1.58	-0.77	0.31
$\dot{V}O_{2,}$max/kg (z-score)	-0.25 ± 1.28	-0.68	0.18
$\dot{V}E,CO_2$ (L/min)	31.1 ± 5.6	29.2	33.0
Stc,O_2 (%)	95.3 ± 3.0	94.1	96.5
Exercise duration (z-score)	0.79 ± 1.2	0.40	1.18

Linear regression analysis showed that the $\dot{V}O_2$ max z-score was positively associated with FEV_1 z-score before BD ($R^2 = 0.27$; $p = 0.001$), after correction for duration of ventilation, parental smoking, sport practise and exercise tolerance.

DISCUSSION

We found mild to moderate pulmonary function abnormalities in children and adolescents born with high risk CDH compared to a matched control group. Linear regression analysis revealed that GERD in the first 2 years after repair was an independent determinant of a reduced FEV_1 and FVC. Furthermore, our study demonstrated that the majority of patients had a normal exercise capacity and cardiorespiratory response.

A reduced FEV_1, FVC, FEV_1/FVC and MMEF was found in almost half of the CDH survivors, versus approximately 0% in the control group. Obstructive airways disease in these patients may be due to distorted airway architecture due to pulmonary hypoplasia or ventilator-induced barotrauma. When comparing CDH patients who were ventilated less than 7 days with patients ventilated more than 7 days we found a significantly lower FEV_1 after bronchodilation in the latter group, which may reflect severity of (CDH related) pulmonary disease or ventilator-induced barotrauma. This finding is in agreement with earlier studies.[14;25] The increased RV/TLC ratio might be due to obstructive impairment. However, it has been demonstrated that the size of the alveoli themselves increases, resulting in alveolar distension and consequently hyperinflation [6;13], which may also cause an increased RV/TLC ratio.[25;26] Overall CDH patients appeared not to have an important reduction of total lung capacity in their school and adolescent years.[25-27]

It has been suggested that delayed CDH repair and lung-protective ventilation strategies might prevent ventilator-induced lung injury.[4;8] Nonetheless our results are similar to those of the study of IJsselstijn *et al.* in which CDH patients were operated immediately after birth implying that neonatal management, particularly ventilation strategy, is not a major determinant of long term lung function in high risk CDH.[25]

Nine children had significant bronchodilator responsiveness. Only two of these children were currently treated with inhaled steroids and/or B2-mimetics. All children had shortness of breath, though they did not experience this as abnormal. This suggests that both parents and physicians tend to underestimate the significance of respiratory symptoms in children born with CDH. This might be due to their willingness to accept symptoms that they assume are due to the underlying congenital abnormality in the lung as well as the fact that many patients have been living with obstructive airway pathology since birth and might therefore not fully apprehend their respiratory limitations. This phenomenon has been previously reported.[27]

Linear regression analysis demonstrated that GERD in the first 2 years after repair was an independent predictor for a reduction in FEV_1. An association between airway obstruction and GERD has been suggested before, but is controversial.[28] It may be speculated that prolonged microscopic aspiration of gastric acid into the airways, and potentially into the alveoli, may cause chronic pulmonary inflammation and pulmonary fibrosis. Schachter *et al.* found that adult patients with severe GERD have a reduced diffusion capacity compared to patients without GERD.[29] There are no pulmonary function studies describing the long term follow-up of infants with severe GERD, although it has been reported that children born with esophageal atresia and radiologically demonstrated gastro-esophageal reflux in early childhood had airway obstruction more often, and smaller lung volumes, 6-37

years after repair of esophageal atresia compared to children born with esophageal atresia without gastro-esophageal reflux.[30]

Despite the pulmonary function abnormalities, all children except three reached a normal $\dot{V}O_{2,}max$.. It should be noted, however, that results in nine patients were excluded and eight patients could not perform the CPET. We cannot exclude possible selection bias regarding the CPET, since patients with the poorest pulmonary function did not perform the test.

The reduced $\dot{V}O_{2,}max$ in three patients is most probably due to airway abnormalities. A reduced $\dot{V}O_{2,}max$ due to a decreased level of fitness is less likely, because two of the three patients practised sports twice a week.

Our study demonstrated that the majority of patients tested had a normal exercise capacity and cardiorespiratory response. Mean duration of CPET was even longer than expected. During exercise four children had mild desaturation with a normal O_2 pulse and $\dot{V}E,CO_2$ indicating that measurement of saturation was unsatisfactory due to perspiration and movement.

We studied a relatively large group of school aged high risk CDH survivors. Although our control group was not recruited specifically for this study, measurements were made in similar age-groups and with comparable techniques. The cohort had similar neonatal characteristics compared to those survivors who did not participate. We therefore infer that the results from our cohort are representative of the entire group of surviving CDH patients that present with early respiratory symptoms.

We recognize that, despite using z-scores based on a healthy reference population for the CPET, a control group is preferable. Another limitation is the broad age range of the studied patients, which is almost inevitable due to the relatively low incidence of CDH and the high mortality. We used z-scores to compensate for the age difference.

In conclusion, we demonstrated that survivors of high risk CDH have mild to moderate pulmonary function abnormalities, which might be related to GERD in the first years after CDH repair. Future research is recommended in order to investigate the relation between GERD after CDH repair and pulmonary function abnormalities in later life.

Exercise capacity and oxygen uptake is probably normal in these patients, indicating that they are not at risk of developing long term pulmonary vascular pathology. Nevertheless our results demonstrate that periodical evaluation of cardiorespiratory function in all CDH survivors is mandatory with particular attention for the role of GERD as subjects tend to underestimate their symptoms.

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LIST OF ABBREVIATIONS

AS	Apgar score
BD	Bronchodilation
CDH	Congenital diaphragmatic hernia
CI	Confidence interval
CPET	Cardiopulmonary exercise testing
ECCS	European community for coal and steel
ECMO	Extracorporal membrane oxygenation
ERS	European respiratory society
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GERD	Gastroesophageal reflux disease
IVC	Inspiratory vital capacity
Ln	Natural logarithm
MMEF	Maximal midexpiratory flow
PEF	Peak expiratory flow
PPHN	Persistent pulmonary hypertension of the neonate
RER	Respiratory exchange ratio
RV	Residual volume
SD	Standard deviation
Stc,O_2	Transcutaneous oxygen saturation
TLC	Total lung capacity
$\dot{V}E$	Minute ventilation

$\dot{V}E,CO_2$	Ratio of ventilation to CO_2 output
$\dot{V}O_2,max$	Maximal oxygen uptake

Reference List

1. Vanamo, K. A 45-Year Perspective of Congenital Diaphragmatic Hernia. Br.J.Surg. 1996;83(12):1758-62.

2. Colvin, J., Bower, C., Dickinson, J. E., and Sokol, J. Outcomes of Congenital Diaphragmatic Hernia: a Population-Based Study in Western Australia. Pediatrics 2005;116(3):e356-e363.

3. Stege, G., Fenton, A., and Jaffray, B. Nihilism in the 1990s: the True Mortality of Congenital Diaphragmatic Hernia. Pediatrics 2003;112(3 Pt 1):532-5.

4. Sakurai, Y., Azarow, K., Cutz, E., Messineo, A., Pearl, R., and Bohn, D. Pulmonary Barotrauma in Congenital Diaphragmatic Hernia: a Clinicopathological Correlation. J.Pediatr.Surg. 1999;34(12):1813-7.

5. Beals, D. A., Schloo, B. L., Vacanti, J. P., Reid, L. M., and Wilson, J. M. Pulmonary Growth and Remodeling in Infants With High-Risk Congenital Diaphragmatic Hernia. J.Pediatr.Surg. 1992;27(8):997-1001.

6. Hislop, A. and Reid, L. Persistent Hypoplasia of the Lung After Repair of Congenital Diaphragmatic Hernia. Thorax 1976;31(4):450-5.

7. Wilson, J. M., Lund, D. P., Lillehei, C. W., and Vacanti, J. P. Congenital Diaphragmatic Hernia--a Tale of Two Cities: the Boston Experience. J.Pediatr.Surg. 1997;32(3):401-5.

8. Azarow, K., Messineo, A., Pearl, R., Filler, R., Barker, G., and Bohn, D. Congenital Diaphragmatic Hernia--a Tale of Two Cities: the Toronto Experience. J.Pediatr.Surg. 1997;32(3):395-400.

9. Bos, A. P., Hussain, S. M., Hazebroek, F. W., Tibboel, D., Meradji, M., and Molenaar, J. C. Radiographic Evidence of Bronchopulmonary Dysplasia in High-Risk Congenital Diaphragmatic Hernia Survivors. Pediatr.Pulmonol. 1993;15(4):231-4.

10. Shehata, S. M., Sharma, H. S., van der Staak, F. H., van, de Kaa-Hulsbergen, Mooi, W. J., and Tibboel, D. Remodeling of Pulmonary Arteries in Human Congenital Diaphragmatic Hernia With or Without Extracorporeal Membrane Oxygenation. J.Pediatr.Surg. 2000;35(2):208-15.

11. Shehata, S. M., Tibboel, D., Sharma, H. S., and Mooi, W. J. Impaired Structural Remodelling of Pulmonary Arteries in Newborns With Congenital Diaphragmatic Hernia: a Histological Study of 29 Cases. J.Pathol. 1999;189(1):112-8.

12. Muratore, C. S., Kharasch, V., Lund, D. P., Sheils, C., Friedman, S., Brown, C., Utter, S., Jaksic, T., and Wilson, J. M. Pulmonary Morbidity in 100 Survivors of Congenital Diaphragmatic Hernia Monitored in a Multidisciplinary Clinic. J.Pediatr.Surg. 2001;36(1):133-40.

13. Falconer, A. R., Brown, R. A., Helms, P., Gordon, I., and Baron, J. A. Pulmonary Sequelae in Survivors of Congenital Diaphragmatic Hernia. Thorax 1990;45(2):126-9.

14. Stefanutti, G., Filippone, M., Tommasoni, N., Midrio, P., Zucchetta, P., Moreolo, G. S., Toffolutti, T., Baraldi, E., and Gamba, P. Cardiopulmonary Anatomy and Function in Long-Term Survivors of Mild to Moderate Congenital Diaphragmatic Hernia. J.Pediatr.Surg. 2004;39(4):526-31.

15. Arena, F., Baldari, S., Centorrino, A., Calabro, M. P., Pajino, G., Arena, S., Ando, F., Zuccarello, B., and Romeo, G. Mid- and Long-Term Effects on Pulmonary Perfusion, Anatomy and Diaphragmatic Motility in Survivors of Congenital Diaphragmatic Hernia. Pediatr.Surg.Int. 21-10-2005;1-6.

16. Smeets, M., Brunekreef, B., Dijkstra, L., and Houthuijs, D. Lung Growth of Pre-Adolescent Children. Eur.Respir.J. 1990;3(1):91-6.

17. Schrader, P. C., Quanjer, P. H., van Zomeren, B. C., de Groodt, E. G., Wever, A. M., and Wise, M. E. Selection of Variables From Maximum Expiratory Flow-Volume Curves. Bull.Eur.Physiopathol.Respir. 1983;19(1):43-9.

18. Quanjer, P. H., Tammeling, G. J., Cotes, J. E., Pedersen, O. F., Peslin, R., and Yernault, J. C. Lung Volumes and Forced Ventilatory Flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur.Respir.J.Suppl 1993;16:5-40.

19. Newth, C. J., Enright, P., and Johnson, R. L. Multiple-Breath Nitrogen Washout Techniques: Including Measurements With Patients on Ventilators. Eur.Respir.J. 1997;10(9):2174-85.

20. Stanojevic, S., Wade, A., Stocks, J., Hankinson, J., Coates, A. L., Pan, H., Rosenthal, M., Corey, M., Lebecque, P., and Cole, T. J. Reference Ranges for Spirometry Across All Ages: a New Approach. Am.J.Respir.Crit Care Med. 1-2-2008;177(3):253-60.

21. Sterk, P. J., Quanjer, P. H., van Zomeren, B. C., Wise, M. E., and van der, Lende R. The Single Breath Nitrogen Test in Epidemiological Surveys; an Appraisal. Bull.Eur.Physiopathol.Respir. 1981;17(3):381-97.

22. Bruce, R. A., Kusumi, F., and Hosmer, D. Maximal Oxygen Intake and Nomographic Assessment of Functional Aerobic Impairment in Cardiovascular Disease. Am.Heart J. 1973;85(4):546-62.

23. ATS/ACCP Statement on Cardiopulmonary Exercise Testing. Am.J.Respir.Crit Care Med. 15-1-2003;167(2):211-77.

24. Binkhorst, RA, Hof van 't, MA, and Saris, WHM, maximale inspanning door kinderen; referentiewaarden voor 6-18 jarige meisjes en jongens. Den Haag: Nederlandse Hart Stichting; 1982.

25. IJsselstijn, H., Tibboel, D., Hop, W. J., Molenaar, J. C., and de Jongste, J. C. Long-Term Pulmonary Sequelae in Children With Congenital Diaphragmatic Hernia. Am.J.Respir.Crit Care Med. 1997;155(1):174-80.

26. Marven, S. S., Smith, C. M., Claxton, D., Chapman, J., Davies, H. A., Primhak, R. A., and Powell, C. V. Pulmonary Function, Exercise Performance, and Growth in Survivors of Congenital Diaphragmatic Hernia. Arch.Dis.Child 1998;78(2):137-42.

27. Trachsel, D., Selvadurai, H., Bohn, D., Langer, J. C., and Coates, A. L. Long-Term Pulmonary Morbidity in Survivors of Congenital Diaphragmatic Hernia. Pediatr.Pulmonol. 2005;39(5):433-9.

28. Field, S. K., Underwood, M., Brant, R., and Cowie, R. L. Prevalence of Gastroesophageal Reflux Symptoms in Asthma. Chest 1996;109(2):316-22.

29. Schachter, L. M., Dixon, J., Pierce, R. J., and O'Brien, P. Severe Gastroesophageal Reflux Is Associated With Reduced Carbon Monoxide Diffusing Capacity. Chest 2003;123(6):1932-8.

30. Chetcuti, P., Phelan, P. D., and Greenwood, R. Lung Function Abnormalities in Repaired Oesophageal Atresia and Tracheo-Oesophageal Fistula. Thorax 1992;47(12):1030-4.

Legends to figures

Figure 1. Exclusion and enrolment of the patients

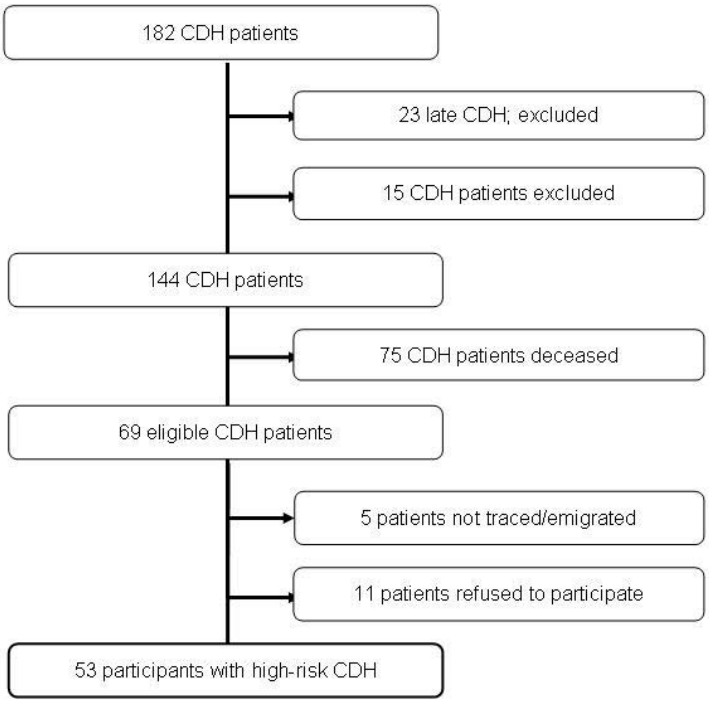
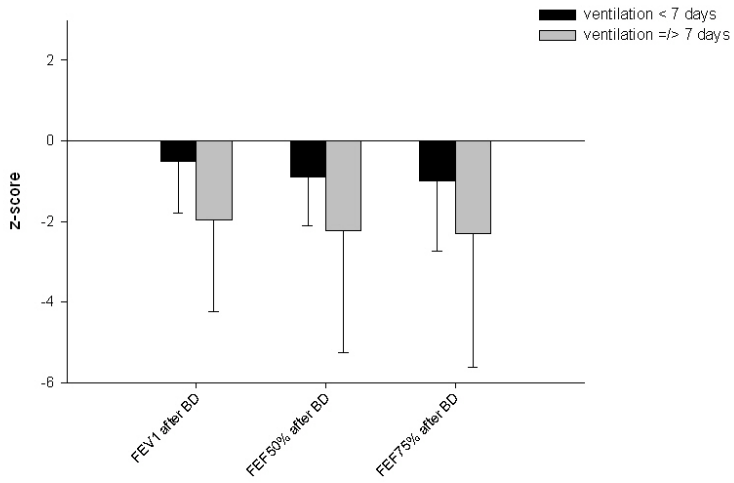


Figure 2. Comparison of pulmonary function parameters in patients ventilated at least 7 days *vs* patients ventilated less than 7 days (2A) and patients requiring antireflux surgery *vs* no antireflux surgery (2B). All lung function parameters are expressed as z-score according to Stanojevic [20].

BD : bronchodilation; FEV1: forced expiratory volume in one second; MMEF: midmaximum expiratory flow; FVC: forced vital capacity.

2A


ventilation < 7 days
ventilation =/> 7 days
z-score
2
0
-2
-4
-6
FEV1 after BD
FEF50% after BD
FEF75% after BD

2B

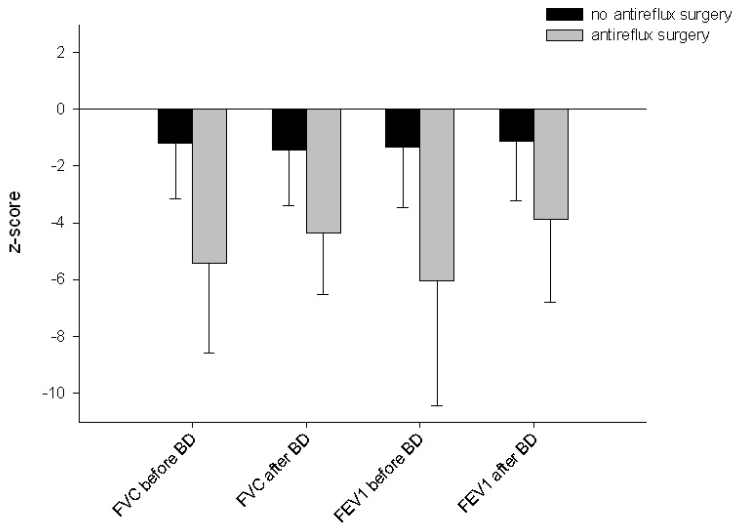
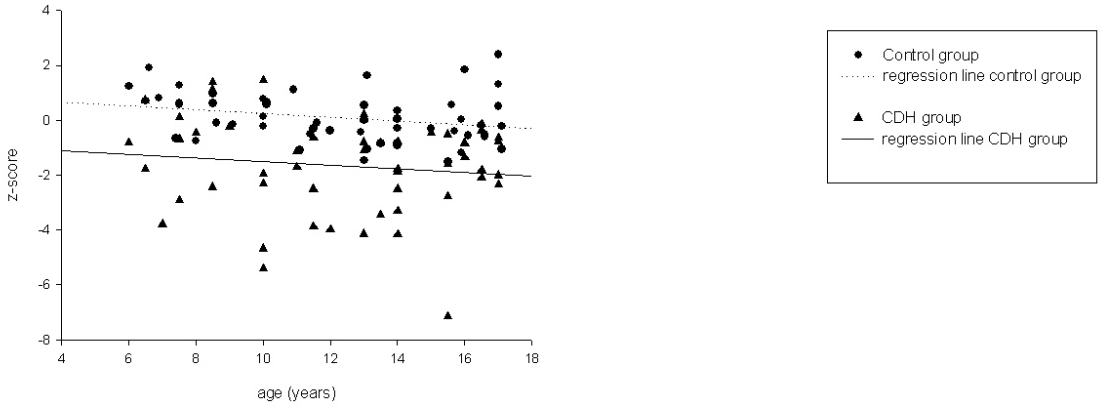
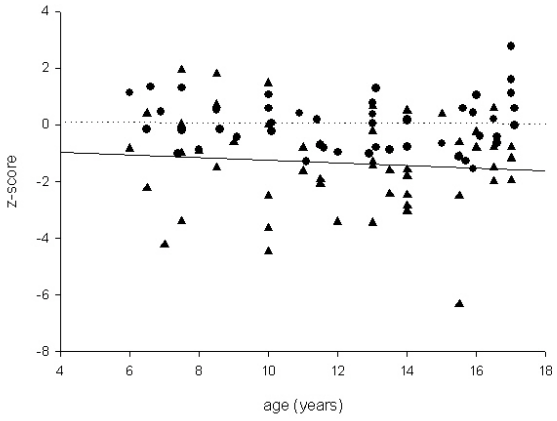

no antireflux surgery
antireflux surgery
z-score
2
0
-2
-4
-6
-8
-10
FVC before BD
FVC after BD
FEV1 before BD
FEV1 after BD

Figure 3. Relation between lung function results and age at follow-up. Thick and dotted lines represent regression lines derived from data of the control group and the CDH group respectively. Lung function results are expressed as z-scores according to Stanojevic *et al.*[20].

FEV$_1$



FVC



FEV$_1$/FVC