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Pulmonary function and exercise capacity in survivors of congenital diaphragmatic hernia

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ABSTRACT: 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 h) and to explore the relationship of these findings with CDH severity.

Of 159 patients born with high-risk CDH, 84 survived. Of the 69 eligible patients, 53 children (mean±SD age 11.9±3.5 yrs) underwent spirometry, lung volume measurements and maximal cardiopulmonary exercise testing (CPET). Results of the pulmonary function tests were compared with those from a healthy control group matched for sex, age and height.

CDH survivors had a significantly lower forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), FEV_1/FVC, maximum mid-expiratory flow and peak expiratory flow when compared with healthy controls. The residual volume/total lung capacity ratio was significantly higher. Linear regression analysis showed that gastro-oesophageal reflux disease was an independent determinant of reduced FEV_1 and FVC. CPET results were normal in those tested.

High-risk CDH survivors have mild to moderate pulmonary function abnormalities when compared with a healthy matched control group, which may be related to gastro-oesophageal 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.

KEYWORDS: Congenital diaphragmatic hernia, exercise capacity, follow-up, pulmonary function testing

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Congenital diaphragmatic hernia (CDH) is a life-threatening anomaly with a mortality rate ranging 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, characterised 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 remodelling 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 with healthy children [12–15] and when compared with 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 yrs who had undergone

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surgical repair of high-risk CDH in the neonatal period. Results of the pulmonary function tests were compared with 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 Paediatric Surgical Centre of Amsterdam (the Netherlands) between 1987 and 1999, and to the Sophia Children's Hospital in Rotterdam (the Netherlands) between 1988 and 1994, were eligible for this study. Children who were treated at the Sophia Children's Hospital after 1994 or treated with extracorporeal membrane oxygenation (ECMO) since 1991 were included in another follow-up programme 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 of all three participating hospitals (VU University Medical Centre, Amsterdam; Academic Medical Centre, Emma Children's Hospital, Amsterdam; and Erasmus Medical Centre, Sophia Children's Hospital, Rotterdam). Written informed consent was obtained from all patients and their parents or guardians prior to inclusion.

Patients' charts were reviewed, focusing on relevant peri- and post-natal variables.

Study design

Patients who gave informed consent attended the outpatient clinic for a study visit. Pulmonary function testing included spirometry and lung volume measurements were followed by cardiopulmonary exercise testing (CPET).

For the pulmonary function test, patients were matched for height, age and sex with schoolchildren and adolescents that had been studied independently in the past. The studies of Dutch schoolchildren [16] and 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 nonsmokers.

Pulmonary function tests

Patients performed standard spirometry and underwent lung volume measurements according to the guidelines of the European Coal and Steel Community (ECSC)/European Respiratory Society (ERS) [18]. All medication was discontinued 24 h prior to testing. Forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), maximum mid-expiratory 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 4×100 μg salbutamol aerosol, in order to evaluate the reversibility of potential bronchial obstruction and prevent exercise-induced bronchoconstriction. A change in FEV_1 $\geqslant 12\%$, 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.* [20] did not provide reference values for the PEF, these results were expressed as $L \cdot s^{-1}$. The RV/TLC ratio was expressed as a percentage. Z-scores < -1.64 (fifth percentile of the reference population) were considered abnormally low.

In the matched controls all measurements were obtained without bronchodilation. Flow–volume curves were obtained *via* a dry rolling-seal spirometer in children and with a Fleisch III pneumotachometer in adolescents (both Vica Test 5, Mijnhardt, the Netherlands). In adolescents, but not in schoolchildren, RV 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 females and 361 males. Regression equations were derived that gave the best fit to the data (table 1).

Cardiopulmonary exercise testing

Maximal exercise capacity was assessed using the Bruce treadmill test. The Bruce test protocol calls for 3-min stages of increasing belt speed and per cent grade on a treadmill (Marquette, 2000 treadmill; Marquette Electronics Inc., Milwaukee, WI, USA) [22]. Children were always tested in the presence of their parent(s). Each patient was allowed to familiarise themselves with the mouthpiece and the treadmill during a 3-min period prior to the start of the test. Each child was

TABLE 1 Regression equations derived from the data of growing children [16]

Index	Equation	R^2	RSD
Females			
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
Males			
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

These regression equations were used to calculate the z-scores for the lung volume measurements. Height is expressed in cm and age in years. RSD: residual standard deviation; ln: natural logarithm; RV: residual volume; TLC: total lung capacity.

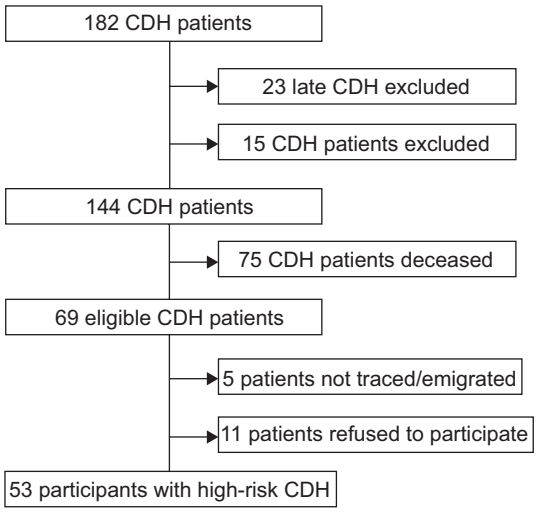

FIGURE 1. Exclusion and enrolment of the patients. CDH: congenital diaphragmatic hernia.

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 (V'_E), maximal oxygen uptake ($V'_{O_2,max}$), oxygen pulse (*i.e.* oxygen uptake divided by the heart rate), respiratory exchange ratio, ratio of V'_E to carbon dioxide production (V'_{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).

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), respiratory exchange ratio >1.0 during 1 min or exhaustion of the subject [23].

The $V'_{O_2,max}$ and the $V'_{O_2,max}$ per 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 zero as reference for normally distributed continuous data. The Kolmogorov–Smirnov test was used to determine whether results were normally distributed. Nonparametric tests were used for non-normally distributed continuous data. The Fisher exact test or the Chi-squared test was used for comparing categorical data. To explore the relationship 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 (SPSS Inc., Chicago, IL, USA) was used for data analysis.

RESULTS

Patient characteristics

In total, 182 patients born with CDH were referred to the Paediatric Surgical Centre of Amsterdam between 1987 and 1999, and the Sophia Children's Hospital in Rotterdam between 1988 and 1994; 84 of them survived. 15 patients were excluded because of treatment with ECMO (seven patients), mental retardation (three patients), trisomy 21 (two patients), pentalogy of Cantrell (one patient), pulmonary haemosiderosis (one patient) and missing patient files (one patient).

Of the 69 high-risk CDH patients eligible for this study, 53 (77%) agreed to participate (fig. 1). 33 patients were treated in the Paediatric Surgical Centre of Amsterdam and 20 in the Sophia Children's 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 nonparticipating patients did not differ significantly

	Participating	Nonparticipating	p-value
Subjects n	53	16	
Male	29 (55)	9 (56)	1.00
Birth weight g	3198±670	3076±450	0.52
Gestational age weeks	38.9±2.2	39.4±1.7	0.75
AS after 5 min ⩽5	8 (15)	2 (13)	1.00
Symptoms ⩽6 h after birth	45 (85)	13 (81)	1.00
Left-sided CDH	45 (85)	16 (100)	0.22
Ventilation days	8.0 (1–66)	13.0 (0–36)	0.61
Patch reconstruction	19 (36)	7 (44)	0.63
Asthma in history	15 (28)	3 (19)	0.53
GORD in history#	19 (36)	8 (50)	0.40
Cardiac abnormalities	8 (15)	5 (31)	0.15
Recurrent CDH	5 (9)	1 (6)	1.00

Data are presented as n (%), mean±SD or median (range), unless otherwise stated. AS: Apgar score; CDH: congenital diaphragmatic hernia; GORD: gastro-oesophageal reflux disease. #: GORD was demonstrated by gastrointestinal radiography series, pH measurement and/or endoscopy in the first 2 yrs after CDH repair.

The mean±SD of 2.8±3.7 days (median 2 days, range 0–23 days) after birth. CDH repair was only performed when patients were stabilised and adequately oxygenated. Lung-protective ventilation strategies were used in both neonatal care units. Median hospital stay was 24 days (range 10–330 days).

Four children were born before a gestational age of 36 weeks (minimum 31 weeks). CDH repair was performed a mean±SD

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

Persistent pulmonary hypertension of the neonate was well documented in only seven (13%) cases, while in many files accurate information was missing. One patient was discharged with oxygen, which was continued for 3 months after discharge.

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

TABLE 3 Results of the spirometry and lung volume measurements of the congenital diaphragmatic hernia (CDH) patients

	CDH		Controls		p-value	95% CI of the difference
	Mean±SD	Range	Mean±SD	Range		
Before bronchodilation						
Spirometry						
Subjects n	48		48			
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 $L \cdot s^{-1}$	4.89±1.79	1.42–8.23	6.45±2.10	3.16–10.34	<0.001	-2.34– -0.78
After bronchodilation						
Spirometry						
Subjects n	38					
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 $L \cdot s^{-1}$	5.38±1.80	2.36–9.02				
Lung volumes						
Subjects n	48		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

Data are expressed as z-scores calculated from a reference population [20], unless otherwise stated. CI: confidence interval; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; MMEF: maximum mid-expiratory flow; PEF: peak expiratory flow; TLC: total lung capacity; RV: residual volume.

Pulmonary function

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

TABLE 4 Stepwise multivariate regression models for several pulmonary function parameters

	B	SE	p-value	Adjusted R^2
FEV_1 before bronchodilation#				
Early GORD	-1.29	0.385	0.002	0.19
Constant	-0.73	0.243		
FVC before bronchodilation#				
Early GORD	-1.536	0.438	0.001	0.10
Constant	-0.932	0.277		
FVC after bronchodilation#				
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		

Independent variables were duration of ventilation, early gastro-oesophageal reflux disease (GORD; <2 yrs after congenital diaphragmatic hernia correction), side of defect, asthma in first grade family members, atopy and parental smoking. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity. #: expressed as z-scores.

Z-scores of all pulmonary function test results were normally distributed. The FEV_1 z-score before bronchodilation was abnormally low (< -1.64) in 22 (46%) CDH patients, compared with zero subjects 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 (25%) out of 48 CDH patients the FEV_1/FVC z-score was abnormally low (< -1.64) before bronchodilation, compared with three (6%) subjects in the control group ($p=0.007$). Mean FEV_1, FVC, FEV_1/FVC, MMEF and PEF were significantly lower in CDH patients compared with the control group (table 3).

The RV/TLC ratio z-score was > +1.64 in 25 (52%) patients, compared with zero subjects in the control group ($p<0.001$); in 19 (76%) this was due to an elevated RV, in five (20%) to a decreased TLC, and in one (4%) patient to a combination.

Restrictive impairment (TLC z-score < -1.64) was demonstrated in eight (17%) patients, compared with zero subjects in the control group ($p=0.02$).

Linear regression analysis disclosed a negative association between gastro-oesophageal reflux disease (GORD) and both FEV_1 and FVC before bronchodilation (table 4). Patients who were ventilated for ⩾7 days had significantly lower z-scores

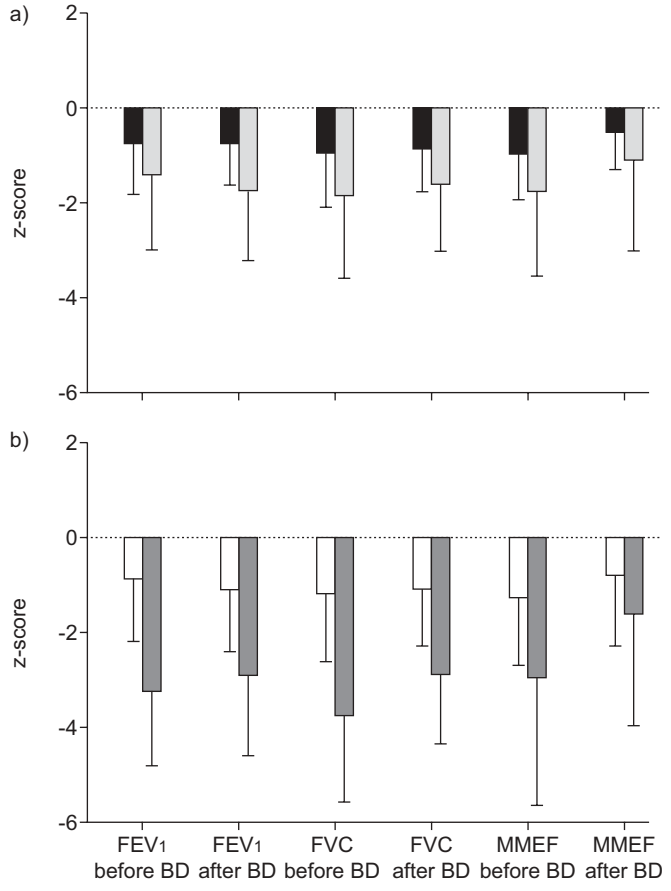

FIGURE 2. Comparison of pulmonary function parameters in a) patients ventilated for ⩾7 days (▒) *versus* patients ventilated <7 days (■) and b) patients requiring antireflux surgery (■) *versus* no antireflux surgery (□). All lung function parameters are expressed as z-scores according to STANOJEVIC *et al.* [20]. FEV1: forced expiratory volume in 1 s; BD: bronchodilation; FVC: forced vital capacity; MMEF: maximum mid-expiratory flow.

for FEV1 after bronchodilation and FVC before bronchodilation (fig. 2a). Patients who had undergone antireflux surgery had significantly lower z-scores for FEV1, FVC, MMEF (fig. 2b) and TLC. There was a trend towards higher age at follow-up and lower z-scores for FEV1 (p=0.051; fig. 3a) and FEV1/FVC (p=0.06; fig. 3c) in CDH patients. There was no association between age and the z-score for FVC (p=0.22; fig. 3b).

Maximum exercise testing

Eight patients did not perform CPET for the following reasons: refusal (five patients), technical problems (two patients) and severely impaired pulmonary function (FEV1 z-score -7.14; one patient). Pulmonary function results were significantly lower for patients who did not perform the CPET (FEV1 z-score -3.93 *versus* -1.10; p=0.002; and FEV1/FVC z-score -2.49 *versus* -0.76; p=0.02).

In total, 45 patients underwent CPET. The results of nine patients were excluded from analysis because they did not reach the level of maximal exercise due to painful legs (six patients), mild motor skills disorder (one patient), shortness of breath (one patient) and being too small to fulfil the protocol

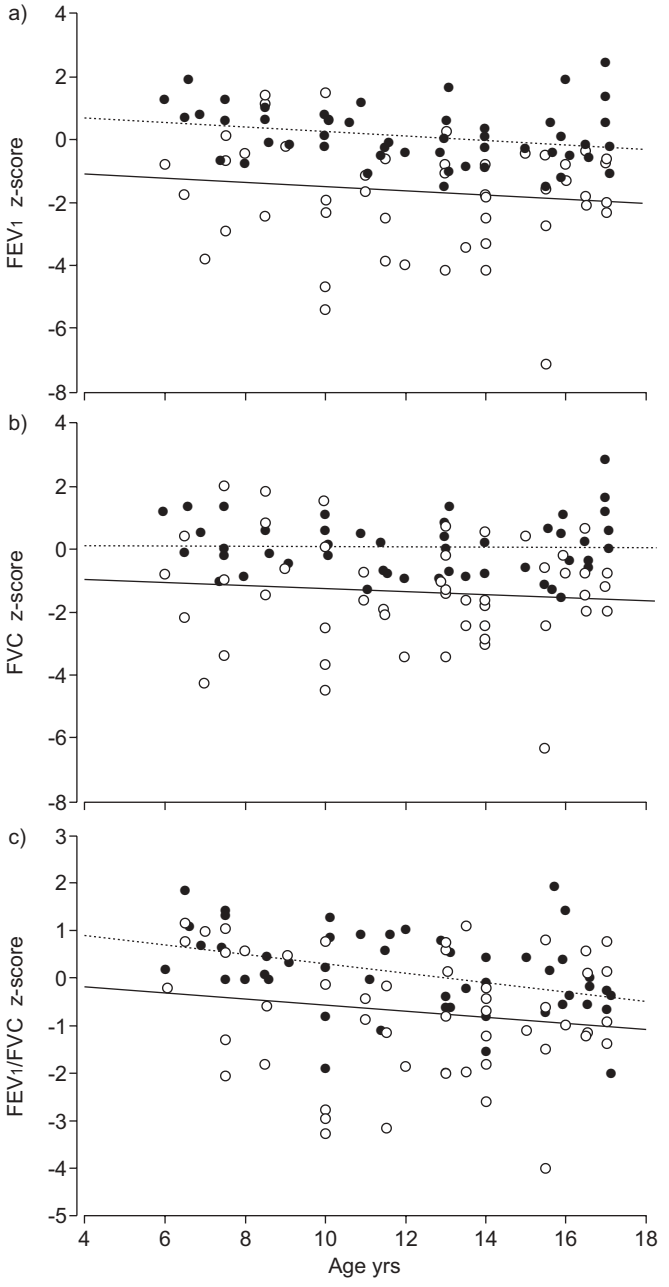

FIGURE 3. Relationships between lung function results and age at follow-up. Lung function results are expressed as z-scores according to STANOJEVIC *et al.* [20]. FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity. ●: control group; ○: congenital diaphragmatic hernia (CDH) group; ——: regression lines derived from data of the control group; ·····: regression lines derived from data of the CDH group.

(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 (transcutaneous oxygen saturation 84–94%) during CPET; two 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 $\dot{V}'O_{2,max}$

TABLE 5 Results of the cardiopulmonary exercise testing

Parameter	Mean±SD	95% CI
f_C max % pred	97.7±1.3	96.4–99.4
f_R max breaths·min^{-1}	57.9±14.4	53.0–62.9
Respiratory exhange ratio	1.09±0.13	1.05–1.13
V'_E max L·min^{-1}	71.4±26.8	62.3–80.4
Oxygen pulse % pred	102.7±17.1	96.4–108.9
$V'_{O_2,max}$ z-score	-0.23±1.58	-0.77–0.31
$V'_{O_2,max}$ per kg z-score	-0.25±1.28	-0.68–0.18
V'_E/V'_{CO_2} L·min^{-1}	31.1±5.6	29.2–33.0
S_{tc,O_2} %	95.3±3.0	94.1–96.5
Exercise duration z-score	0.79±1.2	0.40–1.18

CI: confidence interval; f_C: cardiac frequency; f_R: respiratory frequency; V'_E: minute ventilation; $V'_{O_2,max}$: maximal oxygen uptake; V'_{CO_2}: carbon dioxide production; S_{tc,O_2}: transcutaneous oxygen saturation.

z-score (< -1.96). In one child this was accompanied by a reduced peak oxygen pulse (oxygen pulse ⩽80% predicted), whereas two patients had airway obstruction (FEV1/FVC z-score -2.80 and -2.00). Overall, the mean±SD $V'_{O_2,max}$ z-score did not differ significantly from normal values (-0.23±1.58; p=0.39; table 5).

Linear regression analysis showed that the $V'_{O_2,max}$ z-score was positively associated with FEV1 z-score before bronchodilation (R^2=0.27; p=0.001), after correction for duration of ventilation, parental smoking, sport practice and exercise tolerance.

DISCUSSION

We found mild to moderate pulmonary function abnormalities in children and adolescents born with high-risk CDH compared with a matched control group. Linear regression analysis revealed that GORD in the first 2 yrs after repair was an independent determinant of a reduced FEV1 and FVC. Furthermore, our study demonstrated that the majority of patients had a normal exercise capacity and cardiorespiratory response.

Reduced FEV1, FVC, FEV1/FVC and MMEF were found in almost half of the CDH survivors, compared with ~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 for <7 days with patients ventilated for ⩾7 days, we found a significantly lower FEV1 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 TLC 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.* [25], in which CDH patients were operated on immediately after birth, implying that neonatal management, particularly ventilation strategy, is not a major determinant of long-term lung function in high-risk CDH.

Nine children had significant bronchodilator responsiveness. Only two of these children were currently treated with inhaled steroids and/or β-mimetics. All children had shortness of breath, although 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 GORD in the first 2 yrs after repair was an independent predictor for a reduction in FEV1. An association between airway obstruction and GORD 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.* [29] found that adult patients with severe GORD have a reduced diffusion capacity compared with patients without GORD. There are no pulmonary function studies describing the long-term follow-up of infants with severe GORD, although it has been reported that children born with oesophageal atresia and radiologically demonstrated GORD in early childhood had airway obstruction more often, and smaller lung volumes, 6–37 yrs after repair of oesophageal atresia, compared with children born with oesophageal atresia without GORD [30].

Despite the pulmonary function abnormalities, all children except three reached a normal $V'_{O_2,max}$. 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 $V'_{O_2,max}$ in three patients is most probably due to airway abnormalities. A reduced $V'_{O_2,max}$ 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 oxygen pulse and V'_E/V'_{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 with 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 recognise 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 GORD in the first years after CDH repair. Future research is recommended in order to investigate the relationship between GORD 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 to the role of GORD, as subjects tend to underestimate their symptoms.

STATEMENT OF INTEREST

None declared.

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