

# **Congenital diaphragmatic hernia and exercise capacity, a longitudinal evaluation**

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## ABSTRACT

### *Objective*

Children with congenital diaphragmatic hernia (CDH) suffer from long-term pulmonary morbidity. Longitudinal data of exercise capacity in these children are lacking. We hypothesized that exercise capacity would be impaired in children with CDH and deteriorates over time. We evaluated exercise capacity and its determinants in CDH patients longitudinally until 12 years of age.

### *Design*

Prospective longitudinal follow-up study in tertiary university hospital.

### *Patients*

One hundred and fourteen children with CDH born between 1999-2012.

### *Methods*

Exercise capacity was evaluated using the Bruce treadmill-protocol at the ages of 5, 8 and 12 years. Primary outcome parameter was standard deviation score (SDS) of maximal endurance time. Data were analyzed by using linear mixed models.

### *Results*

A total of 107 children (30 treated with extracorporeal membrane oxygenation [ECMO]) performed 191 reliable exercise tests. At ages 5, 8 and 12 years, the mean (95% CI) SDS endurance time was -0.44 (-0.65 to -0.24); -1.01 (-1.23 to -0.78); -1.10 (-1.40 to -0.80) respectively, all less than zero ( $p < 0.001$ ). Exercise capacity declined significantly over time irrespective of ECMO-treatment (5 to 12 years: non-ECMO  $p = 0.015$ ; ECMO  $p = 0.006$ ). Duration of initial hospital stay and diffusion capacity corrected for alveolar volume were associated with SDS endurance time ( $p < 0.001$  and  $p = 0.039$ ).

### *Conclusions*

In CDH patients exercise capacity deteriorates between 5 and 12 years of age, irrespective of ECMO-treatment. CDH patients may benefit from long-term assessments of exercise capacity with timely intervention.

## INTRODUCTION

Congenital diaphragmatic hernia (CDH) occurs in 1 in 3000-4000 births.<sup>1</sup> Although CDH is still a life-threatening anomaly, survival rates have increased over the past decades.<sup>2</sup> Advances in surgical and neonatal management, as well as the implementation of a standardized European neonatal treatment protocol in November 2007<sup>3</sup> (Table 1 of the supplemental file), have significantly contributed to higher survival rates<sup>2</sup> which turned out to be sustainable over time and in many centers around the world. With the increased survival, more children may suffer from long-term morbidities, including pulmonary symptoms. Factors that may contribute to long-term pulmonary morbidity are lung hypoplasia with persistent airflow obstruction,<sup>4,5</sup> iatrogenic lung damage due to mechanical ventilation,<sup>4</sup> and microstructural changes in the lung.<sup>6</sup> These pulmonary abnormalities may lead to decreased exercise capacity on the long-term and affect development in later life. While several studies found decreased exercise capacity in CDH patients at school-age,<sup>7-11</sup> a few other studies showed normal exercise capacity in school-aged<sup>5,12</sup> and in adult CDH patients.<sup>13,14</sup> These studies had mostly a cross-sectional study design, small sample sizes, and included patients born before a standardized postnatal treatment protocol became available. A longitudinal evaluation of exercise capacity in CDH patients has not been performed to date.

Therefore, the aim of the present study was to evaluate longitudinally exercise capacity at the ages of 5, 8 and 12 years in a large cohort of CDH patients treated with or without neonatal extracorporeal membrane oxygenation (ECMO). Secondly, we aimed to find clinical determinants of exercise capacity. Furthermore, we evaluated whether the implementation of a standardized postnatal treatment protocol influenced exercise capacity.

## MATERIALS AND METHODS

### Patients, procedures and study design

We included all CDH patients born between January 1999 and May 2012 who joined our prospective, multidisciplinary follow-up program at the Erasmus MC-Sophia Children's Hospital. This program conforms to the present standard of care for children born with major anatomical congenital anomalies, including ECMO treatment if needed. In this program, the children and their parents are followed by a multidisciplinary team, and eight standardized assessments are performed between 0.5 and 17 years of age.<sup>10,15</sup>

We excluded data from patients diagnosed with CDH after seven days of age, those with paraesophageal diaphragmatic defects, those with a diaphragmatic eventration, and those with psychomotor disabilities who could not perform a maximal cardiopul-

monary exercise test. Until November 2007, ECMO treatment was applied in cases of reversible severe respiratory failure by using the entry criteria reported by Stolar et al.<sup>16</sup> After November 2007, children were treated according to the standardized CDH EURO Consortium consensus treatment protocol<sup>3</sup> which included similar ECMO criteria (Table 1 of the supplemental file).

A pediatrician and a pediatric surgeon performed standardized physical examination. Exercise capacity was evaluated by an experienced pediatric physical therapist. Standardized information (type and frequency of sports participation other than gymnastics) was recorded about sports participation. Prior to the exercise test, parents estimated their child's fitness level as higher, equal to or less than that of children with the same age. Perinatal and demographic characteristics were retrieved from medical records. The last included patient was tested in July 2017.

The Medical Ethics Committee of the Erasmus MC stated that the rules laid down in the Medical Research Involving Human Subjects Act and did not apply to this research proposal (MEC-2016-111). Parents of all children were routinely informed about the study and provided permission to use the data for research purposes.

## Measurements

### *Baseline data*

The following baseline data were recorded: gender, age, gestational age, birth weight, ethnicity, side hernia, type of repair, duration of mechanical ventilation, ventilation-free days in the first 28 days of life, type of initial mechanical ventilation, duration of intensive care unit (ICU) stay, duration of initial hospital stay, presence of chronic lung disease (CLD),<sup>17</sup> congenital cardiac anomalies, treatment with phosphodiesterase type 5 inhibitor, and sports participation. Moreover, we assessed lung function. Forced expiratory volume in 1 s (FEV<sub>1</sub>) was assessed with an electronic spirometer (Masterscreen PFT; Carefusion, San Diego, CA) after inhalation of 400 µg salbutamol<sup>18</sup> and expressed as absolute value and as SDS.<sup>19</sup> Total lung capacity (TLC) was determined by whole body plethysmography (Masterscreen Body Plethysmography; Carefusion, San Diego, CA) and expressed as absolute value and percentile score. Diffusion capacity corrected for alveolar volume (K<sub>CO</sub>) was measured using a multigas analyzer (Masterscreen PFT; Carefusion, San Diego, CA) by the single-breath method. Percentile scores for static lung volumes and diffusion capacity obtained by the reference equations of Koopman et al.<sup>20</sup> were transformed into SDS using an inverse normal transformation.

### *Exercise capacity*

All children performed a maximal cardiopulmonary exercise test after the lung function assessment, that is, 1–2 hours after inhalation of salbutamol if applicable. Therefore,

we evaluated only lung function after bronchodilation (BD). The maximal cardiopulmonary exercise test was performed on a motordriven treadmill (En Mill; Enraf Nonius, Rotterdam, the Netherlands), programmed for increases in angle of inclination and speed according to the Bruce protocol.<sup>21,22</sup> The children were encouraged to perform to exhaustion. The maximal endurance time (in minutes, one decimal) served as criterion of exercise capacity, with SDS based on reference values for healthy Dutch children.<sup>21,22</sup> Heart rate and transcutaneous oxygen saturation were monitored before and during the test with a pulse oximeter (MARS [Motion Artifact Reduction System], type 2001; Respironics Novamatrix, Murrysville, PA). Heart rate of  $\geq 185$  beats per min<sup>23</sup> or loss of coordination because of excessive fatigue was taken as maximal performance.

### Statistical analysis

Differences in baseline data between “participants in the follow-up program” and “non-participants in the follow-up program” and the children “treated with neonatal ECMO” and “not treated with neonatal ECMO” were evaluated using Mann-Whitney U tests for continuous variables and chi-square tests for categorical variables. One-sample t-tests were used to test whether the normally distributed data of exercise capacity differed from population norms (SDS = 0). To test whether exercise capacity differed between ECMO treated CDH patients and non-ECMO treated CDH patients, independent samples t-tests were used. Longitudinal evaluation of the endurance times at 5, 8 and 12 years of age was performed using linear mixed-models, which can account for within-subject correlations and allows for missing values in the dependent variable.<sup>24</sup> To investigate whether perinatal and demographic characteristics had a significant influence on SDS endurance time, we considered the following list of baseline data in the linear mixed-model as covariates: gestational age, ECMO treatment, use of a standardized treatment protocol (after November 2007), patch repair, duration of initial hospital stay, ventilator-free days in the first 28 days of life, type of initial mechanical ventilation, congenital cardiac malformation, and sports participation. We used a stepwise backward approach to select covariates from this list of baseline data. Two-way interaction effects were then added to the resulting model if the interaction effect was statistically significant. The results of the linear mixed-models are reported using estimated marginal means, which are the predicted values of the dependent variable adjusted for the effect of covariates. To investigate whether lung function parameters (FEV<sub>1</sub>, TLC, K<sub>CO</sub>) had a significant influence on SDS endurance time, only data of exercise capacity at the ages of 8 and 12 years was used, as lung function was not measured at the age of 5. Therefore, separate linear mixed-models were performed with the above-mentioned list of baseline data and FEV<sub>1</sub>, TLC and K<sub>CO</sub> as covariates at 8 and 12 years of age.

Multicollinearity was assessed using variance inflation factors (VIFs). VIFs  $\leq 5.0$  were considered acceptable, whereas higher values were taken as a sign of multicollinearity.

Spearman's rank correlation was used to test whether the levels of exercise capacity as estimated by the parents was associated with the measured SDS endurance time.

Analyses were performed using SPSS 21.0 (IBM, Chicago, IL, USA), and all statistical tests used a two-sided significance level of 0.05.

## RESULTS

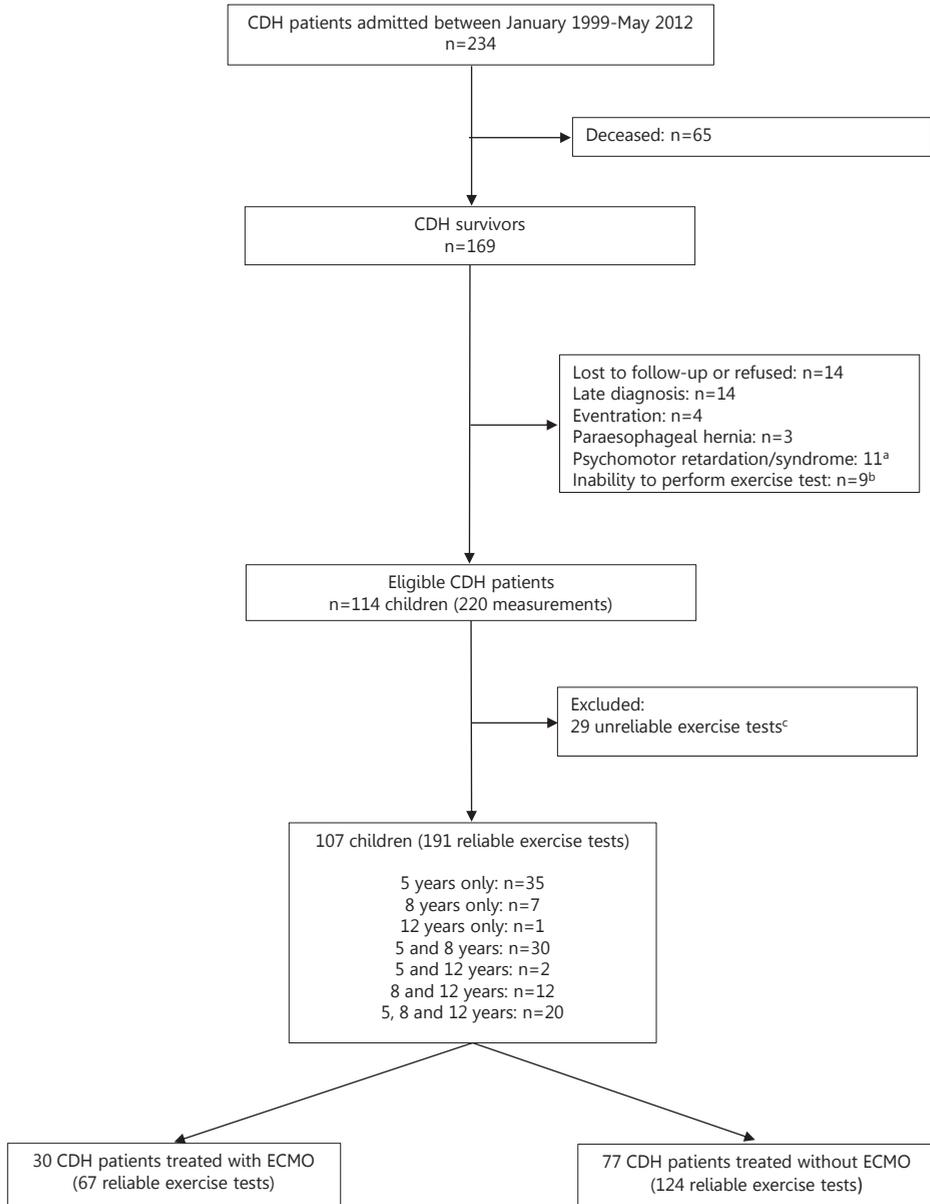
### Patients

Between January 1999 and July 2012, 234 children were born with CDH in the Erasmus MC – Sophia Children's Hospital. Sixty-five (27.7%) died before hospital discharge (Figure 1). Fifty-five (32.4%) of the 169 survivors were excluded for various reasons (Figure 1). Thus, 114 (67.1%) performed the Bruce-protocol (220 measurements). We excluded the results of 29 measurements (13.8%) because maximal performance was not achieved (Figure 1). The analysis for this study concerned 191 reliable tests performed by 107 children (62.9 % of all survivors), of whom 30 (28.0%) had received ECMO treatment.

Patient characteristics are presented in Table 1. Duration of mechanical ventilation, ventilator-free days within the first 28 days of life, PICU stay and duration of initial hospital stay differed significantly between children treated with and without ECMO. Also the presence of CLD, treatment with phosphodiesterase type 5 inhibitor, and FEV<sub>1</sub> after BD (at 8 years of age) were significantly different between these groups (Table 1). No differences in background characteristics, except for ethnicity ( $p=0.001$ ) and birthweight ( $p=0.030$ ), were found between the participants and non-participants of our follow-up program (data not shown).

### Exercise capacity

The estimated marginal mean (95% confidence interval (CI) SDS endurance time was significantly below the norm at all ages: 5 years: -0.44 (-0.65 - -0.24); 8 years: -1.01 (-1.23 - -0.78); 12 years: -1.10 (-1.40 - -0.80) (all  $p<0.001$ ) (Table 3). The mean (SD) heart rate at maximal exercise was 191 (9.0) beats per minute and the median (IQR) transcutaneous oxygen saturation at maximal exercise was 98% (96-99). Exercise capacity decreased significantly from the ages of 5 to 8 years ( $p<0.001$ ) and from 5 to 12 years ( $p<0.001$ ) (Table 2 of the supplemental file).



**Figure 1** - flowchart of the study population selection

<sup>a</sup>Chromosome aberration (n=2), Cohen syndrome (n=1), Loeys-Dietz syndrome (n=1), Simpson-Golabi-Behmel syndrome (n=3), Wolf-Hirschhorn syndrome (n=1), autism (n=3).

<sup>b</sup>Hemiplegia (n=3), aortastenosis (n=1), tracheacanule (n=1), severe chronic lung disease (n=1), organizational reasons (n=2), anxiety (n=1).

<sup>c</sup>Loss of coordination (n=7), anxiety (n=7), refused (n=2), no maximal performance (n=10), loose shoelaces (n=1), insufficient Dutch language (n=1), calf muscle pain (n=1).

CDH = congenital diaphragmatic hernia; ECMO = extracorporeal membrane oxygenation

**Table 1** - Patients characteristics

	Total n=107	ECMO n=30	non-ECMO n=77	p-value
<b>Background</b>				
Gestational age (weeks)	38.6 ± 1.9	39.0 ± 1.6	38.4 ± 2.1	0.105
Birth weight (kilograms)	3.0 ± 0.6	3.2 ± 0.4	3.0 ± 0.6	0.154
Male (%)	62 (57.9)	20 (66.7)	42 (54.5)	0.254
Ethnicity				0.331
Dutch (%)	88 (82.2)	23 (76.7)	65 (84.4)	
Other (%)	19 (17.8)	7 (23.3)	12 (15.6)	
Left-sided hernia (%)	93 (86.9)	27 (90.0)	66 (85.7)	0.555
Patch repair (%)	75 (70.1)	26 (86.7)	49 (63.6)	0.019
Days of mechanical ventilation	11 (6-22)	29 (16-48)	8 (5-16)	<0.001
Ventilator-free days <sup>a</sup>	17 (6-22)	0 (0-12)	20 (12-23)	<0.001
Type of initial mechanical ventilation				0.811
CMV	45 (42.1)	12 (40.0)	33 (42.9)	
HFO	59 (55.1)	17 (56.7)	42 (54.5)	
No ventilation	1 (0.9)	-	1 (1.3)	
Missing	2 (1.9)	1 (3.3)	1 (1.3)	
Days of ICU stay	20 (13-42)	52 (29-80)	16 (10-27)	<0.001
Days of initial hospital stay	36 (20-61)	80 (36-102)	27 (27-50)	<0.001
Chronic lung disease (%)				<0.001
No	68 (63.6)	11 (36.7)	57 (74.0)	
Mild	16 (15.0)	3 (10.0)	13 (16.9)	
Moderate	4 (3.7)	3 (10.0)	1 (1.3)	
Severe	17 (15.9)	13 (43.3)	4 (5.2)	
Missing	2 (1.8)	-	2 (2.6)	
Congenital heart disease <sup>b</sup>	9 (8.8)	5 (16.7)	4 (5.2)	0.055
PDE5 treatment	13 (12.1)	9 (30.0)	3 (3.8)	<0.001

Data are presented as mean ± standard deviation, median (interquartile range) or number (percentage), as appropriate

<sup>a</sup> Ventilator-free days in the first 28 days of life

<sup>b</sup> Congenital heart disease: Ventricle Septum Defect (n=1), Atrium Septum defect (n=2), Ventricle Septum Defect and Atrium Septum Defect (n=1), Double Outlet Right Ventricle + transposition blood vessel + Open Foramen Ovale + Open Ductus Botalli (n=1), Open Ductus Botalli + Open Foramen Ovale + tricuspidalis and mitral insufficiency (n=1), Open Ductus Botalli + Atrium Septum Defect with surgery (n=2), dysplastic pulmonic valve and tricuspidalis insufficiency (n=1)

CMV = conventional mechanical ventilation; ECMO = extracorporeal membrane oxygenation, HFO = high frequency oscillation; ICU = intensive care unit; PDE5 treatment = treatment with phosphodiesterase type 5 inhibitor

**Table 2** - Characteristics at follow-up assessments

At follow-up	Total n=107	ECMO n=30	non-ECMO n=77	p-value
<b>At 5 years of age</b>	n=87	n=23	n=64	
Sports participation (%)	46 (52.9)	14 (60.9)	32 (50.0)	0.373
Referral to PPT <sup>a</sup> (%)	13 (14.9)	4 (17.4)	9 (14.1)	0.703
PPT continuation <sup>b</sup> (%)	8 (9.2)	4 (17.4)	4 (6.3)	0.115
<b>At 8 years of age</b>	n=69	n=26	n=43	
SDS FEV <sub>1</sub>	-0.28 (-1.25 - 0.62)	-1.02 (-1.82 - 0.56)	-0.10 (-0.73 - 0.67)	0.024
SDS TLC	-0.05 (-0.90 - 0.58)	-0.07 (-1.04 - 0.39)	-0.05 (-0.80 - 0.71)	0.576
SDS K <sub>CO</sub>	-1.48 (-2.05 - -0.51)	-1.64 (-2.33 - -0.99)	-1.18 (-1.97 - -0.44)	0.172
Sports participation (%)	54 (78.3)	18 (69.2)	36 (83.7)	0.160
Referral to PPT <sup>a</sup> (%)	20 (28.9)	10 (38.4)	10 (23.7)	0.180
PPT continuation <sup>b</sup>	2 (2.9)	1 (3.8)	2 (4.7)	0.717
<b>At 12 years of age</b>	n=35	n=18	n=17	
SDS FEV <sub>1</sub>	-0.54 (-1.55 - 0.25)	-1.10 (-2.52 - 0.24)	-0.35 (-0.88 - 0.25)	0.136
SDS TLC	0.28 (-0.81 - 1.08)	-0.15 (-1.07 - 0.66)	0.39 (-0.67 - 1.49)	0.159
SDS K <sub>CO</sub>	-1.28 (-1.88 - -0.88)	-1.48 (-2.33 - -0.20)	-1.20 (-1.62 - -0.90)	0.446
Sports participation (%)	24 (68.6)	11 (61.1)	13 (76.5)	0.335
Referral to PPT <sup>a</sup> (%)	10 (28.6)	6 (33.3)	4 (23.5)	0.527
PPT continuation <sup>b</sup> (%)	-	-	-	

Data are presented as median (interquartile range) or number (percentage), as appropriate

<sup>a</sup>After follow-up assessment the patient was referred to a local community based pediatric physical therapist to start intervention

<sup>b</sup>After follow-up assessment the patient was recommended to continue intervention by a local community based pediatric physical therapist.

ECMO = extracorporeal membrane oxygenation; FEV<sub>1</sub> = forced expiratory volume in 1 second; TLC = total lung capacity; K<sub>CO</sub> = diffusion capacity corrected for alveolar volume; PPT = pediatric physical therapist

### ECMO treated CDH patients versus non-ECMO treated CDH patients

Exercise capacity differed significantly between ECMO treated and non-ECMO treated patients (mean difference (95% CI) 0.421 (0.117 - 0.724),  $p=0.007$ ), particularly at the age of 8 ( $p=0.036$ ). Exercise capacity declined significantly in ECMO treated patients from 5 to 8 years ( $p=0.001$ ) and from 5 to 12 years ( $p=0.006$ ). This decline was also seen in non-ECMO treated patients; from 5 to 8 years ( $p=0.008$ ) and 5 to 12 years ( $p=0.015$ ) (Table 3, Figure 2, Table 2 of the supplemental file).

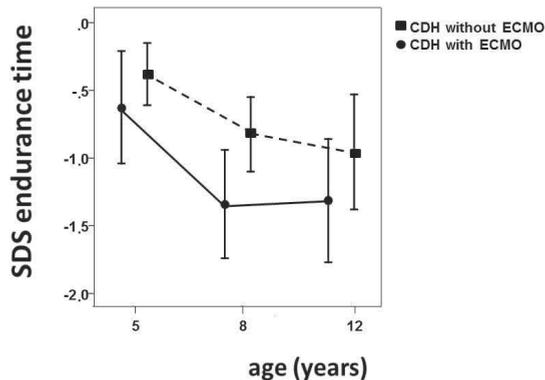
**Table 3** - Endurance time of CDH patients treated with and without ECMO

	5 years	8 years	12 years
All CDH patients, n=107	-0.44 (-0.65 - -0.24) <sup>a</sup>	-1.01 (-1.23 - -0.78) <sup>a</sup>	-1.10 (-1.40 - -0.80) <sup>a</sup>
ECMO, n=31	-0.63 (-1.04 - -0.21) <sup>b</sup>	-1.34 (-1.74 - -0.94) <sup>a</sup>	-1.32 (-1.77 - -0.86) <sup>a</sup>
non-ECMO, n=71	-0.38 (-0.61 - -0.15) <sup>a</sup>	-0.82 (-1.10 - -0.55) <sup>a</sup>	-0.96 (-1.38 - -0.53) <sup>a</sup>

Data are presented as estimated marginal means (95% confidence intervals) SDS endurance time

Significantly below the population norm (SDS = 0): <sup>a</sup>  $p \leq 0.001$ ; <sup>b</sup>  $p = 0.004$

ECMO = extracorporeal membrane oxygenation

**Figure 2** - Change in maximal exercise capacity over time in children with CDH

Data shown are estimated marginal means from the linear mixed model analysis with 95% confidence intervals. CDH = congenital diaphragmatic hernia; ECMO = extracorporeal membrane oxygenation; SDS = standard deviation score

### Associations between exercise capacity and baseline data

Exercise capacity was significantly negatively associated with the duration of initial hospital stay (estimated coefficient [95% CI] -0.006 (-0.009-0.003),  $p < 0.001$ ) and positively with  $K_{CO}$  (estimated coefficient [95% CI] 0.27 (0.01- 0.53),  $p = 0.039$ ). No other significant associations were found between exercise capacity and timepoint of assessment, gestational age, use of a new treatment protocol, patch repair, ventilator free days in the first 28 days of life, type of initial mechanical ventilation, congenital cardiac malformation,  $FEV_1$ , TLC, and sports participation (Table 3 of the supplemental file). Although exercise capacity differed significantly between ECMO treated and non-ECMO treated patients -with lower exercise capacity in ECMO treated patients- ECMO had no significant effect on the deterioration of exercise capacity: no significant interaction-effect was found between ECMO and time point of assessment for exercise capacity ( $p = 0.363$ ). For both groups the same trend in deterioration was observed (Figure 2).

All VIFs were  $\leq 3.1$ .

### Exercise capacity estimated by the parents

The levels of exercise capacity as estimated by the parents correlated positively with the measured SDS endurance time ( $r=0.420$ ,  $p<0.001$ ).

## DISCUSSION

We evaluated longitudinally maximal exercise capacity in children with CDH aged 5 to 12 years. Exercise capacity was significantly below the norm at all ages, and declined significantly over time - not only in children treated with ECMO but also in those who did not need ECMO treatment. The duration of initial hospital stay and the diffusion capacity of the lungs were associated with exercise capacity.

Treatment of neonates with CDH is challenging and therapeutic strategies have changed over the decades. This has resulted in decreasing mortality rates,<sup>2,25</sup> and development of lung protecting strategies, for example, gentle ventilation with permissive hypercapnia.<sup>26</sup> Therefore, it is hard to compare the data of our population with those who survived over 20 years ago.<sup>8,12-14,27,28</sup> We previously found decreased exercise capacity in 5-year-old CDH patients, irrespective of whether they had been treated with ECMO.<sup>10</sup> In another study, in children with different underlying diagnoses, who had all been treated with neonatal ECMO, we showed that maximal exercise capacity was below the norm at 5, 8, and 12 years and deteriorated over time.<sup>11</sup> Many children in that study cohort were born in the early 1990s.<sup>11</sup> Despite the differences in study population, a similar course in deteriorating of exercise capacity was observed in the current study. These findings suggest that exercise capacity should be assessed in childhood and adolescence, and even into adulthood. The question remains, however, whether timely intervention indicated by the assessment outcome may improve or at least prevent deterioration. Encouraging the children to engage in physical activity could help prevent secondary morbidities. Pro-active counselling by physicians and early referral to physical therapists may be useful.

The introduction of the postnatal treatment protocol of the CDH EURO Consortium led to an increased survival of children born with CDH.<sup>3</sup> This protocol was implemented in our department in November 2007. Standardization of postnatal management has resulted in lower mortality but not a lower prevalence of CLD.<sup>2</sup> This suggests that more patients with CDH who develop CLD survive, which may affect maximal exercise capacity. However, we could not demonstrate a significant effect of the introduction of the protocol on maximal endurance time (Tables 3 and 4 of the supplemental file). The effect of improved intensive care might have been counterbalanced by a higher prevalence of survivors with CLD. Larger numbers of children should be studied at 8 and 12 years

to demonstrate a possible effect of the implementation of the treatment protocol on exercise capacity.

We assumed that children with more severe lung hypoplasia, might be at the highest risk for impaired exercise capacity. Indeed, children who had been treated with ECMO had significantly more airflow obstruction and lower SDS endurance time. Interestingly,  $K_{CO}$  was significantly below the norm both in ECMO treated and non-ECMO treated children and was positively associated with exercise capacity, whereas ECMO treatment was not associated with exercise capacity. We speculate that microstructural changes of the lungs, which have been described in young adults with CDH,<sup>6</sup> may already occur at younger age. Future studies focusing on lung structure imaging may be useful to identify patients at risk for clinical deterioration and impaired exercise tolerance. The association between initial hospital stay duration and exercise capacity that we found suggests that the most critically ill neonates with the most severe pulmonary problems are most likely to suffer from persistent pulmonary morbidity later in life.

Besides, we speculate that parents of children who had been critically ill as neonates may consider their child more vulnerable than the parents of the child's healthy peers. For this reason, and also because pulmonary morbidity persist for years,<sup>4,5</sup> parents may not encourage physical activities. This may, in turn, puts them at risk of gross motor function problems<sup>29,30</sup> and consequently reduced participation in physical activities. Smith et al. found similar problems in children born very preterm. Reduced exercise capacity could not be explained by airflow obstruction. Therefore, these authors also hypothesized that children born very preterm are deconditioned and that a lack of physical activity might play a role.<sup>31</sup> Although in our study ECMO treatment had no significant influence on decreased exercise capacity and its deterioration, we assume that the lower exercise capacity in ECMO treated CDH patients might be explained by the fact that ECMO treated patients are the most critically ill children at neonatal age with more severe lung hypoplasia, more airflow obstruction, and less participation in physical activities.

Following this reasoning, the deterioration in exercise capacity between the ages 5 and 8, and its stabilization from the ages of 8, could perhaps partly be explained by sports participation. At the age of 8 and 12 about two-thirds of the children participated in sports versus only half of them at the age of 5. Assumable, parents consider their child in the first years of life more vulnerable and are reluctant to encourage their children in daily physical activities and sports participation.

The main strengths of this study are the longitudinal design within the infrastructure of a standardized follow-up program, the small proportion of children lost to follow-up and the relatively large sample size for this rare congenital anomaly. Some limitations need to be addressed. Not all children participating in the follow-up program had reached the age of 12 years yet. The resulting small number of children assessed at 12 years of

age increases the probability of a type II error, although mixed models account for data missing at random. Secondly, postnatal management of CDH changed during the study period, which could have influenced our results as more children with severe lung hypoplasia survived after introduction of the standardized postnatal treatment protocol. We did not find a significant effect of the introduction of the postnatal treatment protocol on exercise capacity (Tables 3 and 4 of the supplemental file), but larger sample sizes of 8-year-old and 12-year-old children may be needed to detect a significant difference. Thirdly, we used the maximal endurance time rather than the peak oxygen consumption as measure of exercise capacity, mainly for reasons of feasibility. Wearing a mask may lead to loss of cooperation and to submaximal results, especially in the younger children. A strong correlation between maximal endurance time and maximal oxygen uptake has been reported by Cumming and coworkers.<sup>32</sup> Besides, since our setting is an outpatient clinic and not a primary research setting, we feel that cardiopulmonary exercise testing (CPX), which includes breath gas analysis, is too intensive to perform in every CDH patient during routine follow-up. In future research projects in our department, CPX in children will be evaluated, and conclusions on exercise capacity in CDH patients might be extended. Fourthly, we did not include a group of healthy controls. However, we used recently established reference data collected in our own center.<sup>21,22</sup> Fifthly, we had no data on physical activity. Reduced physical activity might be one of the explanations for decreased exercise capacity in children with CDH and is subject of an ongoing research project in our center. Finally, considering the large amount of possible determinants of exercise capacity, as well as the possibility of multicollinearity we had to be critical which lung function parameters to include as possible determinants in the mixed model analysis. In a cross-sectional study of Peetsold and coworkers,<sup>5</sup> exercise capacity and lung function was measured in school-aged children born with CDH and having been referred either to the Paediatric Surgical Centre of Amsterdam (the Netherlands) between 1987 and 1999, and to our center between 1988 and 1994. They showed no associations between  $\text{VO}_2\text{max}$  and lung function parameters, except for  $\text{FEV}_1$  ( $R^2=0.27$ ;  $p=0.001$ ). In another study of our research group none of the lung function parameters, but  $\text{DL}_{\text{CO}}$  was related to  $\text{VO}_2\text{peak \% pred.}$  in young adult CDH patients.<sup>14</sup> Therefore, as multicollinearity arose between lung function parameters in this study, we critically chose to include only  $\text{FEV}_1$ ,  $\text{TLC}$  and  $\text{K}_{\text{CO}}$  in the mixed model analysis.

The significant differences in ethnicity and birthweight between the participants and non-participants in this study was in line with expectations. We found a higher percentage of other ethnicities than Dutch and lower birthweight in the non-participant group. Native Dutch parents and children showed higher follow-up and treatment adherence than parents of other ethnicities.<sup>33</sup> Differences in birthweight between ethnicities are common.<sup>34</sup> Nevertheless, we will pursue our strategies to enhance adherence in non-native Dutch parents and children in our follow-up program. Background characteristics

that reflect severity of illness did not differ between the participants and non-participants (data not shown). Selection bias is likely not present.

## CONCLUSION

CDH patients were at risk for decreased exercise capacity at school-age. Decreased exercise capacity deteriorated over time, not only in children who had needed neonatal ECMO treatment but also in children who had not needed ECMO. Exercise capacity was significantly negatively associated with the duration of initial hospital stay and positively with  $K_{CO}$ . Early risk stratification for decreased exercise capacity may be important to offer timely intervention. Further studies are needed to unravel the causes of decreased exercise capacity. We recommend prolonged follow-up, pro-active advice on physical activities and sports participation or referral to a physical therapist.

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## SUPPLEMENTAL FILE

**Table 1** - Recommendations of the standardized postnatal protocol

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### **Prenatal management and delivery**

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Following prenatal diagnosis, the absolute and O/E LHR and the position of the liver should be evaluated  
Planned vaginal delivery or caesarean section after a gestational age of 37 weeks in a high-volume tertiary center should be pursued

In case of preterm labor prior to 34 weeks of gestation, antenatal steroids should be given

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### **Delivery room management and treatment in a very early phase**

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After delivery, the infant should be intubated immediately without bag and mask ventilation

The goal of treatment in the delivery room is achieving acceptable preductal saturations levels between 80 and 95%

Ventilation in the delivery room may be done by conventional ventilator or ventilation bag with a peak pressure as low as possible, preferably below 25 cm H<sub>2</sub>O

An oro- or nasogastric tube with continuous or intermittent suction should be placed

Arterial blood pressure has to be maintained at a normal level for gestational age. In case of hypotension and/ or poor perfusion, 10- 20 ml/kg NaCl 0.9% should be administered 2 times

Sedatives and analgesics should be given

No routine use of surfactant in either term or preterm infants with CDH

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### **Ventilation management in the Intensive Care Unit**

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Adapt treatment to reach a preductal saturation between 85 and 95% and a postductal saturation above 70%

In individual cases, preductal saturation above 80% might be acceptable, as long as organs are well perfused

The target PaCO<sub>2</sub> range should be between 45 and 60 mmHg

Pressure-controlled ventilation initial settings are a PIP of 20-25 cm H<sub>2</sub>O and a PEEP of 2-5 cm H<sub>2</sub>O; ventilator rate of 40- 60/min

HFOV: initial setting mean airway pressure 13-17 cm H<sub>2</sub>O, frequency 10 Hz, ΔP 30-50 cm H<sub>2</sub>O depending on chest wall vibration

After stabilization, the FiO<sub>2</sub> should be decreased if preductal saturation is above 95%

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### **Further management in the Intensive Care Unit**

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Infants should be sedated and be monitored using validated analgesia and sedation scoring systems

Neuromuscular blocking agents should be avoided if possible

If symptoms of poor perfusion and/or blood pressure below the normal level for gestational age occur and are associated with preductal saturation below 80%, echocardiographic assessment should be performed

In case of hypovolemia, isotonic fluid therapy 10-20 ml/kg NaCl 0.9% up to 3 times during the first 2 hours may be given and inotropics should be considered

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### **Pulmonary hypertension**

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Perform echocardiography within the first 24 h after birth

Blood pressure support should be given to maintain arterial blood pressure levels at normal levels for gestational age

iNO should be considered if there is evidence of extrapulmonary right-to-left shunting and the oxygenation index is above 20 and/or the saturation difference is more than 10%

In case of suprasystemic pulmonary artery pressure and right-to-left shunting through the foramen ovale, i.v. prostaglandin E1 has to be considered

**Table 1** - Recommendations of the standardized postnatal protocol (*continued*)**Extracorporeal membrane oxygenation (ECMO)**

Criteria for ECMO:

- Inability to maintain preductal saturations >85% or postductal saturations >70%.
- Increased PaCO<sub>2</sub> and respiratory acidosis with pH <7.15 despite optimization of ventilatory management.
- Peak inspiratory pressure >28 cm H<sub>2</sub>O or mean airway pressure >17 cm H<sub>2</sub>O is required to achieve saturation >85%.
- Inadequate oxygen delivery with metabolic acidosis as measured by elevated lactate ≥5 mmol/l and pH <7.15.
- Systemic hypotension, resistant to fluid and inotropic therapy, resulting in urine output <0.5 ml/kg/h for at least 12- 24 hours
- Oxygenation index (mean airway pressure x FiO<sub>2</sub> x 100/PaO<sub>2</sub>) ≥40 consistently present

**Surgical repair**

Surgical repair of the diaphragmatic defect should be performed after physiological stabilization, defined as follows:

- Mean arterial blood pressure normal for gestation;
- Preductal saturation levels of 85- 95% on fractional inspired oxygen below 50%;
- Lactate below 3 mmol/l;
- Urine output more than 2 ml/kg/h

No routine chest tube placement

Repair can be performed while the patient is on ECMO

**Fluid management, parenteral feeding, entering enteral feeding and gastroesophageal reflux**

40 ml/kg/day including medication for the first 24 hours after birth, increase intake thereafter

Diuretics should be considered in case of persisting positive fluid balance, aim for diuresis 1- 2 ml/kg/hour

Preventive antireflux therapy should be started in combination with enteral feeding

Reiss, I., et al., Standardized postnatal management of infants with congenital diaphragmatic hernia in Europe: the CDH EURO Consortium consensus. *Neonatology*, 2010. 98(4): p. 354-64.

**Table 2** - Estimated mean differences of endurance time from 5 to 8 years, 8 to 12 years and 5 to 12 years in CDH patients treated with and without ECMO

Group	5-8 years	8-12 years	5-12 years
All patients,* n=107	-0.56 (-0.81 - 0.31) p<0.001	-0.09 (-0.41 - 0.23) p=0.573	-0.65 (0.97 - 0.33) p<0.001
ECMO, n=31	-0.71 (-0.29 - 0.71) p=0.001	0.02 (-0.47 - 0.43) p=0.941	-0.69 (-1.17 - 0.21) p=0.006
Non-ECMO, n=71	-0.44 (-0.76 - 0.12) p=0.008	-0.14 (-0.60 - 0.33) p=0.562	-0.57 (-1.04 - 0.11) p=0.015

\*all CDH patients with a reliable exercise test

Data are presented as estimated mean differences (95% confidence intervals) SDS endurance time

CDH = congenital diaphragmatic hernia; ECMO = extracorporeal membrane oxygenation; SDS = standard deviation score; n = number of patients

**Table 3** - Possible determinants of exercise capacity

Dependent variable Predictor	Estimated coefficient (95% CI)	p-value
<b>Endurance time</b>		
Postnatal protocol	0.041 (-0.371 - 0.453)	0.844
Ventilation free days	0.003 (-0.026 - 0.033)	0.833
Type of initial mechanical ventilation	-0.056 (-0.428 - 0.316)	0.765
Heart disease	-0.145 (-0.755 - 0.465)	0.638
Gestational age	0.031 (-0.064 - 0.126)	0.520
ECMO	0.124 (-0.269 - 0.516)	0.534
Type of repair	0.173 (-0.204 - 0.550)	0.366
Sports participation	-0.133 (-0.415 - 0.149)	0.353
Duration of initial hospital stay	-0.006 (-0.009 - -0.003)	<0.001
<b>Endurance time</b>		
Ventilation free days	-0.001 (-0.050 - 0.047)	0.951
Postnatal protocol	-0.070 (-0.853 - 0.713)	0.858
Heart disease	-0.205 (-1.296 - 0.886)	0.707
Type of repair	0.135 (-0.451 - 0.722)	0.644
Type of initial mechanical ventilation	-0.129 (-0.637 - 0.380)	0.613
ECMO	-0.166 (-0.738 - 0.406)	0.562
Duration of initial hospital stay	-0.003 (-0.011 - 0.004)	0.387
FEV <sub>1</sub>	-0.115 (-0.314 - 0.083)	0.248
Gestational age	-0.099 (-0.256 - 0.059)	0.215
TLC	0.106 (-0.101 - 0.314)	0.310
Sports participation	0.468 (-0.002 - 0.939)	0.051
K <sub>CO</sub>	0.270 (0.014 - 0.526)	0.039

Data are presented as estimated coefficient (95% confidence intervals) SDS endurance time

CDH = congenital diaphragmatic hernia; ECMO = extracorporeal membrane oxygenation; FEV<sub>1</sub> = forced expiratory volume in 1 second; TLC = total lung capacity; KCO = diffusion capacity corrected for alveolar volume

**Table 4** - Exercise capacity of CDH patients treated with and without the postnatal treatment protocol

	5 years	8 years	12 years
Treated without protocol, n=127	n=41 -0.16 (-0.98 - 0.29)	n=51 -1.10 (-1.48 - -0.46)	n=35 -0.96 (-2.00 - -0.57)
Treated with protocol, n=64	n=46 -0.41 (-1.075 - 0.22)	n=18 -0.69 (-1.53 - -0.09)	n=0 -

Data are presented as median (interquartile range) SDS endurance time

CDH = congenital diaphragmatic hernia; ECMO = extracorporeal membrane oxygenation; SDS = standard deviation score; n = number of patients