Determinants of exercise capacity in school-aged esophageal atresia patients

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ABSTRACT

Background and aims

Data on long-term outcome of exercise capacity in school-aged children with esophageal atresia (EA) are scarce. We evaluated maximal exercise capacity and its relation to lung function. Moreover, we studied other possible determinants of exercise capacity and lung function.

Methods

Exercise capacity of 63 children with EA born 1999-2007 was evaluated at the age of 8 years with the Bruce-protocol. Dynamic and static lung volumes, bronchodilator response and diffusion capacity were measured. Furthermore, perinatal characteristics, hospital admissions for lower respiratory tract infections (RTIs), RTIs treated with antibiotics in the past year, symptoms of gastroesophageal reflux, weight-for-height, and sports participation were evaluated as other potential determinants.

Results

Exercise capacity was significantly below normal: mean (SD) SDS -0.91 (0.97); $p<0.001$. All spirometric parameters were significantly below normal with significant reversibility of airflow obstruction in 13.5% of patients. Static lung volumes were significantly decreased (mean [SD] SDS TLC_{he} -1.06 [1.29]; $p<0.001$). Diffusion capacity corrected for alveolar volume was normal (mean [SD] SDS K_{CO} -0.12 [1.04]). Exercise capacity was positively associated with total lung capacity and negatively with SDS weight-for-height. Spirometric parameters were negatively associated with congenital cardiac malformation, duration of ventilation and persistent respiratory morbidity.

Conclusion

Eight-year-old children with EA had reduced exercise capacity which was only associated with the reduction in TLC_{he} and higher SDS weight-for-height. We speculate that diminished physical activity with recurrent respiratory tract infections may also play a role in reduced exercise capacity. This should be subject to further research to optimize appropriate intervention.

INTRODUCTION

Esophageal atresia (EA) is a congenital anatomical malformation requiring neonatal surgical repair and intensive care treatment. The current mortality rate is 5-9% [1,2] and mortality is mainly related to prematurity and associated anomalies such as severe cardiac malformation.[3] A growing number of survivors reach adulthood, and attention has shifted towards the evaluation of long-term morbidity.[4-7]

Evaluation of long-term morbidity is usually focused on gastro-intestinal and respiratory problems, such as gastroesophageal reflux, wheezing, recurrent episodes of bronchitis and pneumonia.[4-7] Only a few studies have addressed exercise capacity in smaller groups of children with EA and reported normal or slightly decreased exercise capacity at school-age.[4,8,9] We previously showed that five-year-old children with EA had a significantly decreased maximal exercise capacity compared with healthy Dutch children.[10] The determinants of decreased exercise capacity in children with EA have not yet been studied.

Respiratory problems occur throughout different stages of life in patients with EA[11] which may be the result of tracheomalacia, reduced mucocilaliary clearance and lung damage due to recurrent infections and/or (micro)aspiration.[4,12,13] Lung function abnormalities with both obstructive and restrictive patterns have been reported in children aged 6-19 years [5,7,13,14] and adults with EA.[13]

We hypothesized that lung function abnormalities contribute to decreased exercise capacity in school-aged children with EA. Therefore, we evaluated exercise capacity and lung function in a cohort of eight-year-old EA patients who prospectively entered our structured follow-up program. In addition, we investigated potential determinants of exercise capacity and lung function in this group.

MATERIALS AND METHODS

Patients, procedures and study design

We included all EA-patients born between January 1999 and August 2007 who joined our follow-up program at the Erasmus MC-Sophia Children's Hospital. This program is the standard of care for children born with major anatomical congenital anomalies. 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.[15,16] We analysed data of children who had been clinically stable for at least 3 weeks prior to the assessments and who performed both a maximal cardiopulmonary exercise test and reproducible lung function tests.

As data were collected during routine care, subjects were not submitted to any handling and no rules of human behavior were imposed. Institutional review board approval was waived (MEC-2016-111). Families were routinely informed about the study and provided permission to use the de-identified data for research purposes.

A pediatrician and a pediatric surgeon performed specific physical examinations. Lung function was measured by a specialized technician and exercise capacity was evaluated by an experienced pediatric physical therapist. Information was recorded about respiratory complaints (productive or recurrent cough, wheezing, asthma, dyspnea in rest and during exercise, mucus retention), total number of hospital admissions for lower respiratory tract infections (RTIs) confirmed by chest X-ray (CXR), and lower RTIs in the previous year treated with antibiotics prescribed by a family physician, local pediatrician or pediatric pulmonologist, reported signs of tracheomalacia (barking cough, inspiratory stridor, obstructive episode with dyspnea, need for aortopexia or a characteristic flattening of the forced expiratory flow curve), symptoms of gastroesophageal reflux (heartburn, chest pain, regurgitation, nocturnal cough, dysphagia, dysphonia), and sports participation. Perinatal and demographic characteristics were retrieved from medical records.

Measurements

Cardiopulmonary exercise testing

All children performed a maximal cardiopulmonary exercise test after the lung function assessment, i.e. 1–2 hours after inhalation of salbutamol if applicable. A motor-driven treadmill (En Mill; Enraf Nonius, Rotterdam, the Netherlands) was used, programmed for increases in angle of inclination and speed according to the Bruce protocol.[17] 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 recently established reference values for healthy Dutch children.[17] Heart rate and transcutaneous oxygen saturation were monitored with a pulse oximeter (MARS [Motion Artifact Reduction System], type 2001; Respironics Novametrix, Murrysville, PA). Heart rate of ≥185 beats per min[18] or loss of coordination because of excessive fatigue was taken as maximal performance.

Lung Function measurement

Airway patency was assessed with an electronic spirometer (Masterscreen PFT; Carefusion, San Diego, CA) before and after inhalation of 400 µg salbutamol[19] except in children with clinically suspected tracheomalacia and documented deterioration of airflow obstruction after inhaled β2-agonists in the past (deterioration of lung function or clinical deterioration reported by the parents). Children using inhalation medication had been

instructed to stop short-acting β2-agonists 8 h and long-acting β2-agonists 24 h before assessment. Forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), FEV_1/FVC and forced expiratory flows between 25% and 75% of vital capacity (FEF_{25-75}) were expressed as absolute values and as SDS.[20] Reversible airway obstruction was defined as an increase of FEV_1 > 11% after bronchodilators.[21] In addition, helium dilution spirometry was performed to assess total lung capacity (TLC_{he}) and RV/TLC ratio (RV/TLC_{he} ratio).

Total lung capacity (TLC_{pleth}), RV/TLC_{pleth} ratio, and functional residual capacity (FRC_{pleth}) were determined by whole body plethysmography (Masterscreen Body Plethysmography; Carefusion, San Diego, CA) and expressed as absolute values and percentile scores.

Diffusion capacity for carbon monoxide (DL_{CO}) 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.[22] were transformed into SDS using an inverse normal transformation.

The fraction of exhaled NO (FeNO) was measured online using the NIOX analyzer (Aerocrine; Solna, Sweden) according to previously described guidelines and compared with the American Thoracic Society (ATS) cut-off point.[23,24] Equipment and procedures fulfilled European Respiratory Society (ERS) criteria.[19]

Statistical analysis

Differences in medical background variables between the groups "participants" and "non-participants" were evaluated using Mann-Whitney U tests for continuous variables and χ^2-tests for categorical variables. One-sample t-tests were used to test whether the normally distributed data of exercise capacity and lung function parameters differed from population norms (SDS = 0).

Univariable and multivariable linear regression analyses were used to detect possible determinants of exercise capacity, with the SDS endurance time as dependent variable and lung function parameters (SDS), change in FEV_1 after bronchodilation (%), type of EA (with/without fistula), congenital cardiac malformation with surgical correction (yes/no), type of surgical approach for esophageal correction (thoracotomy/thoracoscopy), duration of ventilation (days), Nissen fundoplication (yes/no), symptoms of gastroesophageal reflux (yes/no), total number of hospital admissions for lower RTIs confirmed by CXR, lower RTIs in the last year (yes/no), weight-for-height (SDS), and sports participation (yes/no) as independent variables. These possible determinants, except the lung function parameters and weight-for-height, were also used in univariable and multivariable linear regression analyses with SDS lung function parameters as dependent variable.

To detect possible determinants of exercise capacity, multiple imputation with fully conditional specification and the predictive mean matching method was used to impute missing values of the independent variables (SDS FEV_1 n=5, TLC_{he} n=15, SDS K_{CO} n=29,

symptoms of gastroesophageal reflux n=2). A total of 50 imputed data sets were generated for each multivariable linear regression analysis, and the results were combined across the imputed data sets using Rubin's rules. Multicollinearity in the multivariable linear regression analyses was assessed using variance inflation factors (VIFs). VIFs < 3.0 were considered acceptable.

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 August 2007, 90 newborns with EA were admitted to the intensive care unit of the Erasmus MC- Sophia Children's Hospital. Nine children had died (10.0%) and two were not able to perform the follow-up standardized assessments due to intellectual disability (Trisomy 21). The parents of 13 children refused participation in the follow-up program (14.4%) and six children were lost to follow-up (6.7%). Three children underwent surgery elsewhere and were included at the age of eight years (Figure 1). Perinatal and demographic characteristics did not significantly differ between participants and non-participants (data not shown).

Perinatal and demographic characteristics of the 63 participants are shown in Table 1. Most of them had EA with a distal fistula (85.7%) and the majority underwent a thoracotomy (90.5%). Hospital admissions for lower RTIs confirmed by CXR occurred mainly within the first years of life (in 23/63 children; Table 1). Many children had been treated with antibiotics for RTIs in the past year and had signs of tracheomalacia and complaints suggestive for gastroesophageal reflux (Table 1). The majority of children (79.4%) participated in sports.

Exercise capacity

As reliable results could not be obtained in eight (12.7%) children, due to balance problems or failure to reach maximal exercise performance, we obtained reliable data on exercise capacity for 55 (87.3%) children. The mean (SD) SDS endurance time was significantly lower than in the reference population: -0.91 (0.97); p<0.001. The mean (SD) heart rate at maximal exercise was 188 (12.6) beats per minute. Nine children (16.4%) had a decreased oxygen saturation (median 93%, range 90-94) at maximal exercise performance.

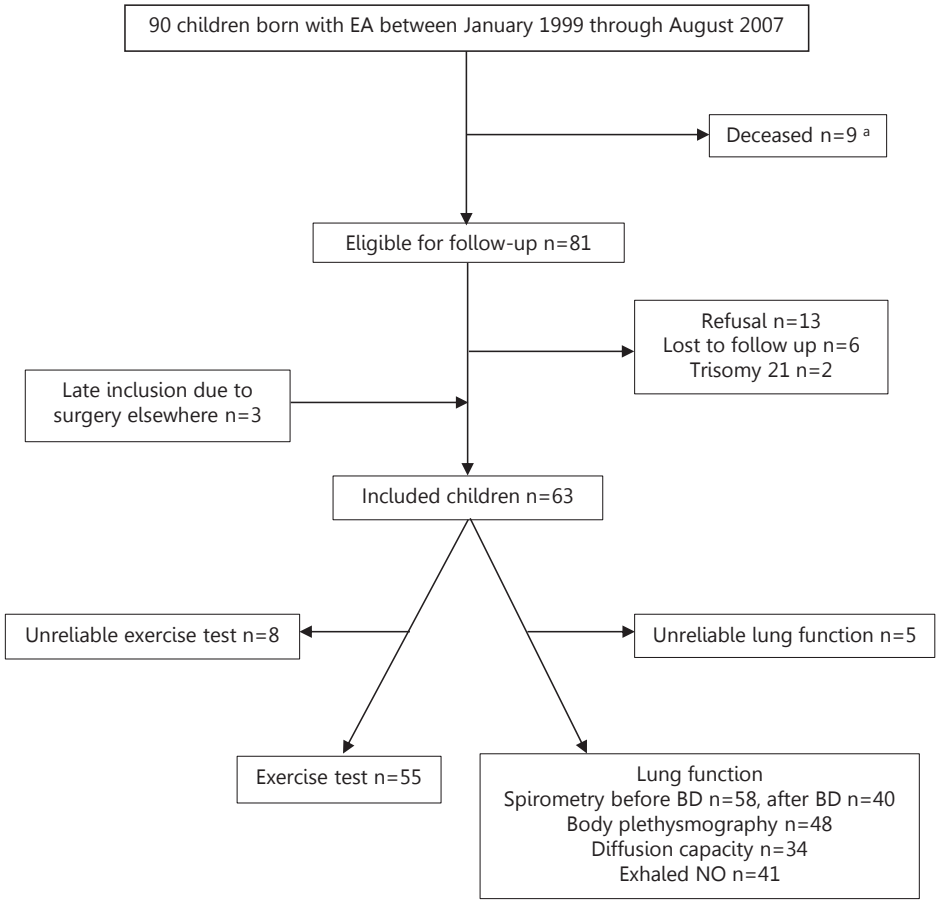

Figure 1 - Inclusion flowchart

[a] deceased due to: major congenital malformation (n=4), sepsis (n=4), respiratory acidosis (n=1)

BD = bronchodilation; NO = nitric oxide

Lung function

Spirometry was measured reliably in 58 (92.1%) of the children, helium dilution spirometry in 48 (76.2%), bodyplethysmography in 41 (65.1%) and diffusion capacity in 34 (54.0%). FeNO was measured reliably in 41 (65.1%) of the children. Missing data were due to unreliable lung function tests in inexperienced children, lack of cooperation, and in one child diffusion capacity could not be obtained because of vital capacity < 1.5L.

Table 1 - Baseline characteristics of participants

Background	**Participants n=63**
Boys, n (%)	36 (57.1)
Gestational age in weeks, median (interquartile range)	38 (36-40)
Small for gestational age (p<3), n (%)	17 (27.0)
Birth weight in kilogram, median (interquartile range)	2.80 (2.1-3.2)
Ethnicity, n (%)	
Dutch	56 (88.9)
Turkish	2 (3.2)
Moroccan	4 (6.3)
Other	1 (1.6)
Type EA, n (%)	
Long gap	5 (7.9)
Distal fistula	54 (85.7)
Proximal fistula	2 (3.2)
Double fistula	1 (1.6)
Long gap with fistula	1 (1.6)
Surgical approach for EA correction, n (%)	
Thoracotomy	57 (90.5)
Thoracoscopy	6 (9.5)
Aortopexy, n (%)	6 (9.5)
VACTERL, n (%)	7 (11.1)
Congenital cardiac malformation,[a] n (%)	10 (15.9)
Cardiac surgerical correction	2 (20)
Ventilatory support in days, median (interquartile range)	2 (2-6)
Chronic Lung Disease, n (%)	4 (6.3)
Nissen fundoplication, n (%)	15 (23.8)
Hospital admissions for lower respiratory tract infections confirmed by chest x-ray, n (%)	23 (36.5)
< 5 years of age	22/63 (34.9)
5 - 8 years of age	4/63 (6.4)
Assessment at 8-years of age	
SDS height, mean (SD)	-0.36 (0.83)
SDS weight-for-height, mean (SD)	-0.26 (0.99)
Respiratory complaints,[b] n (%)	31 (49.2)
Lower respiratory infections past year with antibiotics, n (%)	22 (34.9)
Prophylactic antibiotics	5/22 (22.7)
Therapeutic antibiotics	14/22 (63.6)
>1 therapeutic course	3/22 (13.7)

Table 1 - Baseline characteristics of participants (*continued*)

Background	Participants n=63
Other medication, n (%)	
Bronchodilatator	4 (6.3)
Inhaled corticosteroid	7 (11.1)
Proton pump inhibitor	5 (7.9)
Symptoms of gastroesophageal reflux,[c] n (%)	15 (24.1)
Missing	1 (1.6)
Dysphagia	32 (53.3)
Missing	3 (4.8)
Tracheomalacia,[d] n (%)	25 (39.7)
Scoliosis at physical examination, n (%)	12 (19.0)
Radiologically confirmed scoliosis[e]	8 (12.7)
Sports participation, n (%)	50 (79.4)

Data presented as mean (SD), median (interquartile range) or n (%)

[a] *Cardiac anomalies include: Ventricle Septum Defect (n=4), Atrium Septum Defect (n=1), Atrium Septum Defect and Ventricle Septum Defect (n=1), Coarctation of the aorta (n=2), Patent Foramen Ovale and Atrium Septum Defect (n=1), and Patent ductus ateriosus with Ventricle Septum Defect (n=1). The two children with coarctation of the aorta underwent cardiac surgery;*

[b] *Respiratory complaints: productive cough, recurrent cough, wheezing, asthmatic, dyspnea, recurrent cold;*

[c] *Symptoms of gastroesophageal reflux: heartburn, chestpain, regurgitation, nocturnal cough, dysphagia, dysphonia;*

[d] *Tracheomalacia: barking cough, inspiratory stridor, obstructive episode with dyspnea or a characteristic flattening of the forced expiratory flow curve;*

[e] *Radiologically confirmed scoliosis: mild scoliosis n=6 (Cobb's angle < 10°: n=3 and Cobb's angle 10°-20°: n=3), moderate scoliosis n=2 (Cobb's angle 30° n=1, Cobb's angle 35° after surgery n=1)*

EA= esophageal atresia; VACTER-L stands for vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities

Spirometry results are shown in Figure 2. All spirometry parameters, before and after bronchodilation, were significantly below normal ($p < 0.05$). In 37 children reversibility of airflow obstruction was determined; five of them (13.5%) had clinically relevant increase in FEV_1. Bronchodilation was not provided in 16 children with clinically suspected tracheomalacia (barking cough, inspiratory stridor, obstructive episode with dyspnea or a characteristic flattening of the forced expiratory flow curve) and previous clinical deterioration after bronchodilation and in two other children due to anxiety. Static lung volumes were significantly below normal (Table 2).

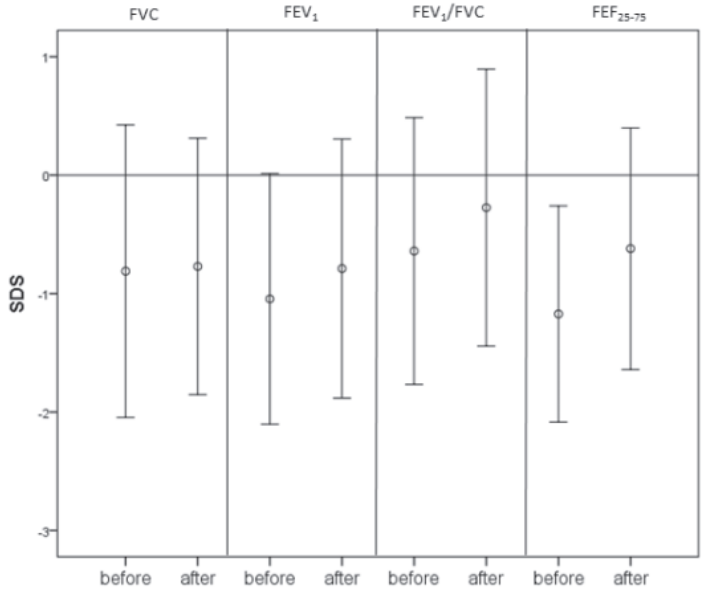

Figure 2 - Spirometry before and after bronchodilation

For all spirometric parameters the mean +/- 1SD is shown. The horizontal axis represents the population mean of healthy children

SDS = standard deviation score, SD = standard deviation; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; FEV_1/FVC = forced expiratory volume in 1 second/ forced vital capacity FEF_{25-75} = forced expiratory flows between 25% and 75% of vital capacity

Median (interquartile range) volume of trapped air (defined as TLC_{pleth} – TLC_{he}) was 0.18 (0.04-0.30) L. Diffusion capacity was normal (Table 2).

The mean (SD) FeNO was 11.49 (6.90) ppb. Thirty-five children (85.4%) had a FeNO <20 ppb, 5/41 (12.2%) 20-35 ppb, and 1/41(2.4%) > 35 ppb.

Table 2 - Lung function at 8 years

	Parameter	Mean (SD) SDS	p-value
Helium dilution spirometry, n=58	TLC_{he}	-1.06 (1.29)[a]	<0.001
	RV/ TLC_{he} ratio	-0.85 (1.54)[a]	<0.001
Bodyplethysmography, n=48	TLC_{pleth}	-1.05 (1.11)[a]	<0.001
	RV/ TLC_{pleth} ratio	0.14 (1.12)	0.441
Diffusion capacity, n=34	DL_{co}	-0.21 (1.29)	0.349
	K_{co}	-0.12 (1.04)	0.520

[a] One sample t-test: p < 0.001 (mean SDS significantly below zero compared with the reference population)

SDS = standard deviation score; SD = standard deviation; TLC_{he} = helium derived total lung capacity; TLC_{pleth} = plethysmographic derived total lung capacity; RV = residual volume; DL_{CO} = diffusion capacity for carbon monoxide; K_{CO} = diffusion capacity corrected for alveolar volume

Determinants of exercise capacity

Moderate to high correlations between the lung function parameters initially led to considerable multicollinearity in the multivariable linear regression analyses with exercise capacity as dependent variable. Therefore, only SDS FEV_1, SDS TLC_{he}, and SDS K_{co} were taken as a measure of airway patency, total lung capacity and diffusion capacity, respectively, and the other lung function parameters were not included as independent variables in the multivariable linear regression analysis. After this adjustment, all VIFs of the predictors were below 3.

Univariable linear regression analyses showed that children with EA without fistula had significantly lower SDS endurance time (p=0.015). This was also confirmed in the multivariate model (p<0.001). In this multivariate model, lower SDS TLC_{he} and higher SDS weight-for-height were significantly associated with lower SDS endurance time (p=0.017 and p=0.007, respectively).

Both univariable and multivariable linear regression analyses showed that exercise capacity was not significantly associated with SDS FEV_1, the percentage change in FEV_1 after bronchodilation, SDS K_{co}, congenital cardiac malformation with surgical correction, type of surgery, duration of ventilation, Nissen fundoplication, symptoms of gastro-esophageal reflux, hospital admissions for lower RTIs confirmed by CXR, RTIs in the past year or sports participation.

See the supplemental file for all results of the univariable and multivariable linear regression analyses.

Determinants of lung function

Univariable linear regression analyses showed significantly more airflow obstruction in children who were re-admitted after initial discharge for lower RTIs confirmed by CXR (SDS FVC: p=0.012, SDS FEV_1: p=0.044), or had suffered from lower RTIs in the last year (SDS FVC: p=0.007, SDS FEV_1: p=0.019). Airflow obstruction was also associated with congenital cardiac malformation with surgical correction (SDS FVC: p=0.035) and duration of ventilation (SDS FVC: p=0.006, SDS FEV_1: p=0.002, SDS FEF_{25-75}: p=0.014).

Children with EA without fistula had significantly more airflow obstruction, but higher lung volumes than those with any kind of fistula (SDS FEV_1: p=0.015, SDS TLC_{he}: p=0.034 and TLC_{pleth}: p=0.037).

Children with RTIs in the last year had a significantly lower lung volume than children without RTIs in the last year (TLC_{he}: p=0.003).

Multivariable linear regression analysis confirmed the association between EA without fistula and higher lung volumes (TLC_{he}: p=0.028) and the association between RTIs in the last year and lower lung volumes (TLC_{he}: p=0.028).

No other significant predictors of SDS lung function parameters were observed in the multivariate model. All VIFs for determinants of lung function were below 1.5.

Diffusion capacity was not associated with any of the lung function parameters, and other abovementioned parameters (see the supplemental file).

See the supplemental file for all results of the univariable and multivariable linear regression analyses.

DISCUSSION

The test outcomes showed reduced exercise capacity, airflow obstruction and low lung volumes in these 8-year-old EA-patients assessed within the infrastructure of a standardized longitudinal follow-up program. Exercise capacity did not correlate with airflow obstruction, diffusion capacity, respiratory problems or symptoms of gastroesophageal reflux, but was associated with long-gap EA without fistula, total lung capacity and weight-for-height.

We previously found reduced exercise capacity in 22 five-year-old EA-patients.[10] Seventeen of those children were also included in the current study. Their exercise capacity at both ages was not significantly different (mean difference [SD] = -0.22 [1.22], p = 0.463), suggesting that reduced exercise capacity persists when the children get older.

Studies on exercise capacity in EA-patients are scarce and usually have a cross-sectional design. Zaccara and coworkers studied eight EA-patients using the Bruce protocol at a mean age of 11.6 years. EA-patients had a significantly lower endurance time than controls.[9] Peetsold and coworkers studied 31 EA-patients at a mean age of thirteen years using the Bruce protocol with VO_2-max as outcome with reference values published in 1982. They reported normal SDS for VO_2-max, suggesting normal maximal exercise capacity.[4] Differences in study design may explain differences between these studies and our results. Selection bias might have occurred in the cross-sectional studies performed by Zaccara and Peetsold.

Two groups studied maximal exercise capacity using bicycle ergometry: Montgomery and coworkers found slightly decreased exercise capacity in EA-patients at a mean age of 14 years,[25] whereas Beucher and coworkers found normal VO_2-max at eight years of age.[8] However, data from Beucher were obtained from retrospective chart analysis and 7/31 patients had to be excluded due to submaximal performance.

In our longitudinal follow-up program we prefer to test school-age children on a treadmill because walking and running are the most frequent physical activities in school-aged children. Moreover, treadmill testing is preferred over bicycle ergometry in children because they have relatively underdeveloped knee extensors which is often the limiting factor of the bicycle test.[26]

Children with long-gap EA without a fistula (n=5) had significantly lower SDS endurance time than those with any kind of fistula which was associated with duration

of ventilation. These children had more airflow obstruction and a longer duration of ventilation.

In the present study we found airflow obstruction that was not reversible in 86.5%. Moreover, static lung volumes were significantly below normal and diffusion capacity corrected for alveolar volume was normal. These observations were in concordance with results of previously published studies on long-term lung function in EA-patients.[4,5,7,13,14,25,27-30]

Our finding that airflow obstruction, persistent respiratory morbidity or gastrointestinal morbidity were not associated with reduced exercise capacity is in line with earlier studies.[4,25] The relatively small reduction in lung volume in the children of our cohort (mean SDS TLC -1.06) will probably not fully explain the reduced exercise capacity. Taken together, we assume that other factors may also contribute to reduced maximal exercise capacity.

One could argue that asthma might explain some of the findings, as it affects airway patency and exercise capacity. However, in the present study a high FeNO, which is a biomarker of eosinophilic airway inflammation and a diagnostic test for allergic asthma, was not associated with exercise capacity. Children with tracheomalacia have generally more airflow obstruction than those without tracheomalacia which may lead to poor exercise performance.[31] In our study – usually mild – airflow obstruction was not correlated with exercise capacity. From our data it is not clear whether clinically significant tracheomalacia with recurrent lower RTIs in the first years of life may contribute to physical inactivity and poor exercise capacity at older age.

We speculate that parents of children who had been critically ill as neonates may consider their child more vulnerable than healthy peers. Therefore, combined with recurrent RTI and feeding difficulties within the first years of life and at older age, these children may be less encouraged to engage in physical activities. This may, in turn, put them at risk of gross motor function problems[10,32] and reduced participation in physical activities. Similar problems seem to occur in other survivors of neonatal critical illness.[15,33] This phenomenon has also been described for chronic diseases such as cystic fibrosis, asthma, and congenital heart disease.[34] Future studies should reveal whether exercise programs may of benefit for these children. A randomized controlled trial on the effect of exercise programs in patients who survived neonatal critical illness is currently being performed in our department.

In our study univariable regression analysis showed that respiratory problems in the neonatal period and at later age were predictors of airflow obstruction. In line with this result, Montgomery and coworkers[25] showed that children with persistent respiratory complaints and RTI at older age have more airflow obstruction and restrictive changes than those with mild respiratory symptoms.

In concordance with our findings, Peetsold and coworkers found that anti-reflux surgery in children with EA had no effect on lung function in childhood.[4]

We observed that congenital cardiac malformation with surgical correction was a determinant of low TLC although only two children needed surgical correction (co-arctation of the aorta). It is not clear whether a reduced TLC resulted from the cardiac malformation or from the surgery.

A strength of our study is that all EA-patients were evaluated within the infrastructure of a longitudinal and structured follow-up program using standardized instruments and up-to-date references for maximal exercise capacity[17] and lung function.[22,35] Selection bias is therefore unlikely. Moreover, compared to other studies on exercise capacity in EA-patients the sample size is large.

A limitation is the missing data of lung function which is mainly due to unreliable lung function tests in inexperienced children. We used multiple imputation to overcome this limitation. Another limitation is the lack of data on physical activity. Reduced physical activity might be one of the explanations for decreased exercise capacity in children with EA. Our assumption that parents' reluctance to encourage their child to engage in physical activities contributes to reduced exercise capacity is highly speculative and should be subject to future studies. Lastly, we did not perform standardized evaluations of respiratory symptoms, tracheomalacia, and gastroesophageal reflux disease (GERD) at the age of eight for this cohort. A standardized and validated questionnaire for respiratory symptoms as the Liverpool respiratory symptom questionnaire,[36] may be worthwhile to validate for EA patients in future research.

Robertson and coworkers reported that the proportion of EA patients with tracheomalacia was similar in those with normal and those with abnormal pulmonary function tests.[27] It is unclear how tracheomalacia was established in that study. We decided to exclude tracheomalacia as a possible determinant from regression analyses since we did not objectify tracheomalacie. Bronchoscopy or expiratory CT scans could be considered as means to evaluate the extent of tracheomalacia in EA-patients.[37] However, it is not clear whether this is of clinical benefit for EA-patients.

In our follow-up program we currently assess GERD with esophageal pH-metry at eight years of age, since many children reported non-specific gastrointestinal complaints the prevalence of Barrett esophagitis in young adult EA-patients is high.[38] Further studies in EA-patients should reveal the validity of a standardized questionnaire for GERD such as the PEDSQL-GI module,[39] to study the relation between exercise capacity, lung function and GERD in more detail.

To minimize the risk of recall bias we recorded the number of lower RTI treated with antibiotics only during the past year. We confirmed that lower RTIs with hospital admission in earlier years contributed to long-term lung function abnormalities. RTIs - with and without hospital admission - in earlier years may have also contributed to decreased

physical activity within the first years of life. Digital exchange of information of prescribed antibiotics between family physician, pharmacy and hospital could contribute to reliable monitoring of the individual use of antibiotics over several years.

In conclusion, decreased exercise capacity in children with EA was not explained by lung function abnormalities, except for TLC. The relatively small reduction in TLC could not fully explain their decreased exercise capacity. We speculate that diminished physical activity as a result of a chronic disease state with recurrent RTIs and physical growth failure may be also a determining factor, which should be addressed in multidisciplinary follow-up clinics for EA-patients.

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Supplemental file

Univariable and multivariable linear regression analyses of exercise capacity and lung function parameters

Dependent variables	Univariable linear regression analyses			Multivariable linear regression analyses		
Predictors	**B**	**CI**	**p**	**B**	**CI**	**p**
SDS endurance time						
SDS FVC before BD	0.217	-0.012 - 0.445	0.063			
SDS FEV_1 before BD	0.237	-0.036 - 0.510	0.087	0.052	-0.275 - 0.379	0.756
Change in FEV_1 after BD, %	-0.012	-0.063 - 0.040	0.641			
SDS FEF_{25-75} before BD	-0.017	-0.390 - 0.356	0.926			
SDS TLC_{he}	0.095	-0.135 - 0.325	0.409	0.341	0.062 - 0.619	0.017*
SDS TLC_{pleth}	0.170	-0.096 - 0.435	0.204			
SDS K_{CO}	0.211	-0.112 - 0.533	0.192	0.091	-0.191 - 0.372	0.527
Anomaly with fistula	1.216	0.248 - 2.185	0.015*	1.988	0.927 - 3.049	< 0.001*
Congenital cardiac malformation	-0.407	-1.118 - 0.303	0.256	0.031	-1.548 - 1.610	0.969
Type of surgery; thoracotomy	-0.889	-1.707 - 0.071	0.340	-0.625	-1.379 - 0.129	0.104
Duration of ventilation, days	-0.002	-0.025 - 0.022	0.882	0.011	-0.015 - 0.038	0.404
Nissen fundoplication	0.314	-0.346 - 0.973	0.345	-0.042	-0.739 - 0.654	0.906
Symptoms of gastroesophageal reflux	0.498	-0.123 - 1.120	0.114	0.135	-0.479 - 0.749	0.666
Hospital admissions for lower RTIs confirmed by CXR	0.245	-0.112 - 0.601	0.174	0.134	-0.235 - 0.503	0.477
Lower RTIs in the past year	0.157	-0.408 - 0.723	0.579	0.530	-0.041- 1.100	0.069
SDS weight-for-height	-0.197	-0.468 - 0.073	0.149	-0.385	-0.663 - -0.106	0.007*
Sports participation	0.565	-0.138 - 1.267	0.113	0.622	-0.022 - 1.267	0.058
SDS FVC before BD						
Anomaly with fistula	0.852	-0.418 - 2.123	0.184	0.155	-1.244 - 1.555	0.824
Congenital cardiac malformation	-2.056	-3.963 - -0.148	0.035*	-0.292	-3.041 - 2.458	0.832
Type of surgery; thoracotomy	0.190	-1.099 - 1.480	0.786	-0.013	-1.290 - 1.264	0.984
Duration of ventilation, days	-0.042	-0.071 - -0.012	0.006*	-0.019	-0.065 - 0.028	0.418
Nissen fundoplication	-0.377	-1.240 - 0.485	0.385	-0.074	-1.078 - 0.930	0.883
Symptoms of gastroesophageal reflux	-0.275	-1.092 - 0.542	0.503	-0.014	-0.889 - 0.861	0.974
Hospital admissions for lower RTIs confirmed by CXR	-0.500	-0.883 - -0.116	0.012*	-0.646	-1.434 - 0.142	0.106
Lower RTIs in the past year	-0.983	-1.689 - -0.277	0.007*	-0.627	-1.399 - 0.144	0.109
Sports participation	0.255	-0.667 - 1.176	0.582	0.321	-0.590 - 1.233	0.482
SDS FEV_1 before BD						
Anomaly with fistula	1.364	0.276 – 2.453	0.015*	0.874	-0.311- 2.059	0.145
Congenital cardiac malformation	-1.574	-3.289 - 0.140	0.071	-0.285	-2.613 - 2.043	0.807
Type of surgery; thoracotomy	0.223	-0.923 - 1.369	0.698	0.067	-1.015 -1.148	0.902
Duration of ventilation, days	-0.041	-0.067 - -0.016	0.002*	-0.030	-0.069 - 0.009	0.133
Nissen fundoplication	-0.525	-1.285 - 0.234	0.171	-0.026	-0.876 - 0.824	0.950

Univariable and multivariable linear regression analyses of exercise capacity and lung function parameters *(continued)*

Dependent variables	**Univariable linear regression analyses**			**Multivariable linear regression analyses**		
Predictors	**B**	**CI**	**p**	**B**	**CI**	**p**
Symptoms of gastroesophageal reflux	-0.273	-1.006 - 0.461	0.459	0.025	-0.716 - 0.766	0.946
Hospital admissions for lower RTIs confirmed by CXR	-0.359	-0.707 - -0.010	0.044*	-0.475	-1.143 - 0.192	0.159
Lower RTIs in the past year	-0.771	-1.409 - -0.133	0.019*	-0.466	-1.119 - 0.188	0.158
Sports participation	0.610	-0.195 - 1.416	0.135	0.717	-0.055 - 1.490	0.068
SDS FEF_{25-75} before BD						
Anomaly with fistula	-0.012	-0.922 - 0.899	0.980	-0.517	-1.533 - 0.499	0.310
Congenital cardiac malformation	-0.960	-2.188 - 0.268	0.123	-0.470	-2.263 - 1.322	0.598
Type of surgery; thoracotomy	-0.079	-0.902 - 0.745	0.849	0.036	-0.814 - 0.887	0.931
Duration of ventilation, days	-0.024	-0.043 - -0.005	0.014*	-0.022	-0.051 - 0.009	0.161
Nissen fundoplication	-0.334	-0.923 - 0.256	0.260	-0.141	-0.835 - 0.553	0.683
Symptoms of gastroesophageal reflux	0.316	-0.244 - 0.877	0.262	0.359	-0.256 - 0.975	0.245
Hospital admissions for lower RTIs confirmed by CXR	-0.076	-0.345 - 0.193	0.571	0.053	-0.498 - 0.605	0.846
Lower RTIs in the past year	-0.404	-0.915 - 0.106	0.117	-0.296	-0.860 - 0.267	0.294
Sports participation	0.410	-0.223 - 1.042	0.199	0.532	-0.123 - 1.187	0.109
SDS TLC_{he}						
Anomaly with fistula	-1.955	-3.757 - -0.153	0.034*	-1.954	-3.683 - -0.225	0.028*
Congenital cardiac malformation	-1.962	-4.546 - 0.622	0.133	-2.054	-4.589 - 0.482	0.109
Type of surgery; thoracotomy	-0.240	-1.477 - 0.996	0.697	-0.125	-1.294 - 1.044	0.830
Duration of ventilation, days	-0.027	-0.066 - 0.012	0.165	-0.012	-0.054 - 0.030	0.564
Nissen fundoplication	-0.485	-1.324 - 0.354	0.251	-0.544	-1.442 - 0.353	0.227
Symptoms of gastroesophageal reflux	0.303	-0.708 - 1.314	0.549	0.687	-0.316 - 1.691	0.174
Hospital admissions for lower RTIs confirmed by CXR	-0.262	-0.661 - 0.136	0.192	0.309	-0.503 - 1.121	0.446
Lower RTIs in the past year	-1.162	-1.129 - -0.302	0.003*	-1.056	-1.882 - -0.229	0.014*
Sports participation	0.299	-0.713 - 1.310	0.555	0.039	-0.927 - 1.005	0.936
SDS TLC_{pleth}						
Anomaly with fistula	-1.674	-3.238 - -0.110	0.037*	-1.407	-3.049 - 0.236	0.091
Congenital cardiac malformation	-1.996	-4.215 - 0.223	0.077	-1.985	-4.426 - 0.457	0.107
Type of surgery; thoracotomy	-0.086	-1.287 - 1.116	0.886	0.080	-1.138 - 1.297	0.895
Duration of ventilation, days	0.005	-0.032 - 0.043	0.772	0.002	-0.041 - 0.044	0.932
Nissen fundoplication	0.020	-0.785 - 0.825	0.050	0.069	-0.858 - 0.996	0.880
Symptoms of gastroesophageal reflux	-0.184	-1.191 - 0.823	0.713	0.268	-0.876 - 1.441	0.636
Hospital admissions for lower RTIs confirmed by CXR	-0.315	-0.671 - 0.042	0.082	-0.404	-1.278 - 0.470	0.353
Lower RTIs in the past year	-0.452	-1.204 - 0.300	0.231	-0.022	-0.862 - 0.906	0.960
Sports participation	0.988	-0.054 - 2.029	0.062	0.819	-0.365 - 2.002	0.168

Univariable and multivariable linear regression analyses of exercise capacity and lung function parameters *(continued)*

Dependent variables	Univariable linear regression analyses			Multivariable linear regression analyses		
Predictors	**B**	**CI**	**p**	**B**	**CI**	**p**
SDS K_{CO}						
Anomaly with fistula	0.678	-0.877 - 2.234	0.381	0.699	-0.969 - 2.367	0.396
Congenital cardiac malformation	-0.612	-2.793 - 1.570	0.572	-1.617	-4.095 - 0.861	0.191
Type of surgery; thoracotomy	0.097	-1.477 - 1.671	0.901	0.224	-1.452 - 1.900	0.785
Duration of ventilation, days	0.029	-0.011 - 0.068	0.149	0.021	-0.025 - 0.067	0.361
Nissen fundoplication	0.386	-0.476 - 1.248	0.369	0.578	-0.473 - 1.628	0.267
Symptoms of gastroesophageal reflux	0.330	-0.578 - 1.238	0.464	0.549	-0.517 - 1.615	0.298
Hospital admissions for lower RTIs confirmed by CXR	0.096	-0.308 - 0.500	0.631	0.220	-0.754 - 1.195	0.645
Lower RTIs in the past year	-0.485	-0.287 - 1.258	0.210	0.483	-0.444 - 1.409	0.293
Sports participation	0.323	0.716 - 1.362	0.531	0.511	-0.624 - 1.647	0.362

** = significant association; B = unstandardized regression coefficient; CI = 95% confidence interval for B*
SDS = standard deviation score; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; FEF_{25-75} = forced expiratory flows between 25% and 75% of vital capacity; TLC_{he} = helium derived total lung capacity; TLC_{pleth} = plethysmographic derived total lung capacity; K_{CO} = diffusion capacity corrected for alveolar volume; RTIs = respiratory tract infections
All predictors, except for lung function parameters, duration of ventilation, number of hospital admissions and weight-for-height, are dichotomous variables (yes/no)