In a Gentle Breeze

Pulmonary morbidity in children with anatomical congenital anomalies; long-term effects on exercise capacity and motor function

In een zachte bries

Luchtwegproblemen bij kinderen met aangeboren anatomische afwijkingen; langetermijneffecten op duuruithoudingsvermogen en motoriek

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Movement is a medicine for creating change in a person's physical, emotional, and mental states.

Carol Welch

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General introduction

INTRODUCTION

Intensive care for children is one of the areas of medicine that have undergone significant development in the past decades. High frequency oscillation (HFO), inhaled nitric oxide (NO), and extracorporeal membrane oxygenation (ECMO) are among the new treatment modalities and minimally invasive surgery is an example of improvement in surgical techniques. These new modalities have reduced mortality rates, but sometimes at the cost of more morbidity. Not only the underlying disease itself, but also side effects of the treatment can cause morbidity. Different health care professionals have therefore become more interested in aspects of short-term and long-term morbidity.[1] Among these professionals the pediatric physical therapist is one of the specialists in movement disorders in children. The use of standardized tests is of great help to identify problems at an early stage, so that intervention can be started as soon as necessary.

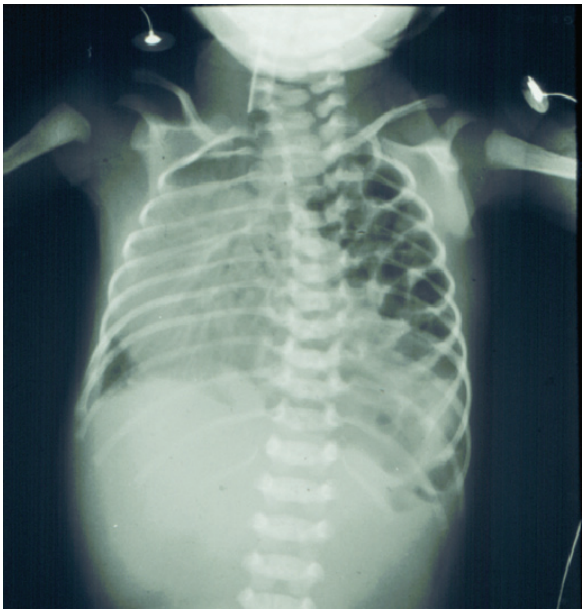
ANATOMICAL CONGENITAL ANOMALIES

Annually some 5,500 newborns (about 3% of all births) in the Netherlands present with major anatomical congenital anomalies (CA).[2] These children often need prolonged hospitalization with (multiple) surgical interventions in the neonatal period and thereafter. Improved antenatal detection, surgical techniques, and peri-operative care have reduced the mortality rates of these anomalies.[3] The pediatric surgeon Ravitch classified six major anatomical congenital anomalies as "index" diagnoses.[4] Those are: congenital diaphragmatic hernia, esophageal atresia, intestinal atresias, Hirschsprung's disease, anorectal malformations, and abdominal wall defects. In the Netherlands, children with index diagnoses are to be treated in a designated pediatric surgical center.[5] In this thesis we have focussed on long-term morbidity in children born with congenital diaphragmatic hernia or esophageal atresia; two pediatric surgical index diagnoses with concomitant abnormal lung development.

Congenital diaphragmatic hernia

Congenital diaphragmatic hernia (CDH) is a congenital anomaly of the diaphragm with an incidence of 1 per 2,500 to 1 per 5,000 live births. It combines a developmental defect of the diaphragm with pulmonary hypoplasia and abnormal pulmonary vaso-reactivity. The defect of the diaphragm leads to herniation of abdominal organs into the chest cavity. The defect is mostly (84% of the cases) located on the left side of the diaphragm. CDH can present as an isolated defect or in combination with other congenital anomalies, such as congenital heart disease or chromosomal anomalies. Mortality rates in live-born patients vary from 10 - 35%. The true mortality may be higher, taking into account antenatal death or termination of pregnancy. Determinants of mortality are the severity of pulmonary hypoplasia, and the presence of pulmonary hypertension. Structural lung alterations are a decrease of the total arteriolar cross-sectional area and a significant wall

thickening in pulmonary arteries of all sizes with abnormal muscularization of the small arterioles, leading to pulmonary hypertension.[6,7] Many CDH survivors face serious morbidity in the first years of life[6,8-11] and later on as well.[12,13]



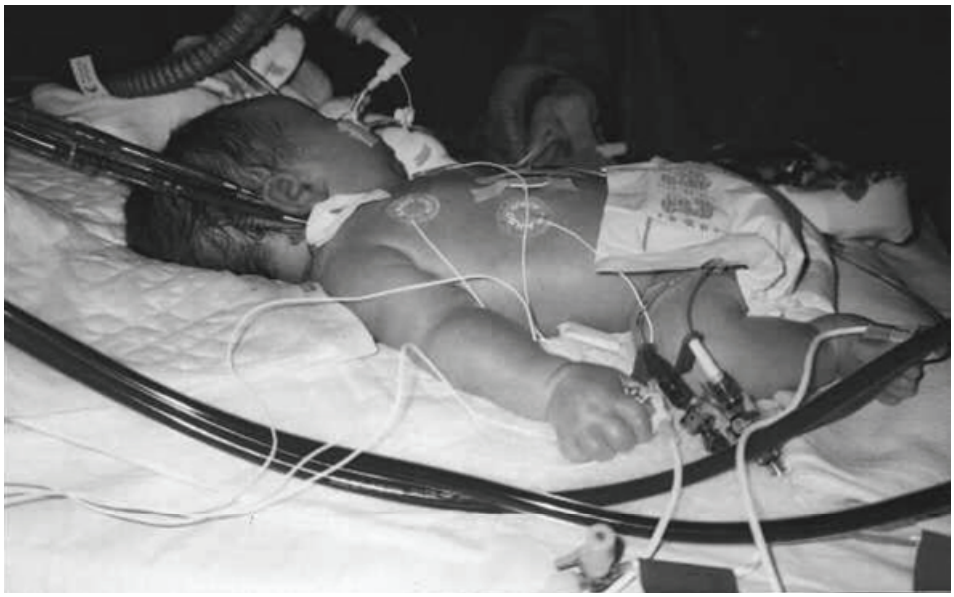
Esophageal atresia

Esophageal atresia (EA) is a congenital developmental defect of the alimentary tract characterized by absence of the normal continuity of the esophagus. It occurs in approximately 1 in 3,500 live births.[14,15] In about half of the cases there are associated anomalies, with cardiac malformations being the most common.[15] Abnormal development of the tracheobronchial tree may contribute to tracheomalacia and recurrent atelectasis.[16] We hypothesized that children after repair of EA show the same extent of respiratory pathologic condition as CDH survivors, with different causative mechanisms.

EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO)

Extracorporeal membrane oxygenation (ECMO) was first used to treat neonatal respiratory failure more than 30 years ago. It is a pulmonary bypass technique providing life support in acute reversible cardiorespiratory failure when conventional management fails. It is thought that this prevents further injury from high oxygen concentration, volutrauma and barotrauma, and hence promotes lung healing.[17] The Erasmus MC-Sophia Children's Hospital Rotterdam and the Radboud University Medical Center Nijmegen are the only two ECMO centers in the Netherlands. In the Sophia Children's Hospital, more than 450 children have been treated with ECMO since 1992 and the overall survival rate is above 75%.

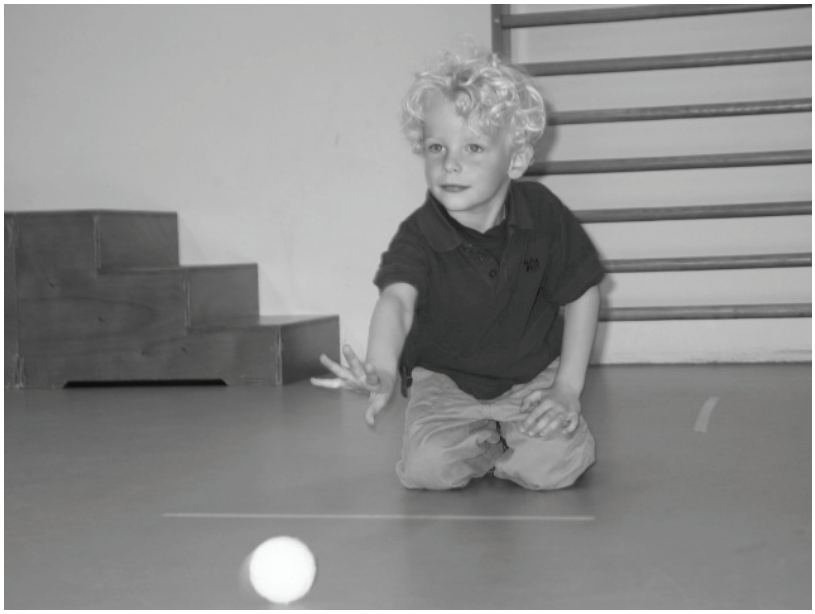
In neonates, ECMO is used predominantly in CDH, meconium aspiration syndrome (MAS), persistent pulmonary hypertension of the newborn, and sepsis. A large trial in the UK on neonatal ECMO conferred a survival advantage of ECMO over conventional management without a concomitant increase in severe disability.[18-20] Thus, ECMO may be of benefit to infants with severe respiratory dysfunction who otherwise would have died. Detailed assessment of long-term morbidity seems therefore essential to confirm the reported survival advantage.[21]



FOLLOW-UP

At the Department of Pediatric Surgery and the Pediatric Intensive Care Unit from the Erasmus MC-Sophia Children's Hospital, we set up a multidisciplinary follow-up program for children born with major anatomical malformations and for their families in January 1999. The program aims to reduce the overall morbidity associated with these malformations, and to offer better care and lines of communication. From 2001 onwards, children treated with ECMO were included in the follow-up program as well. The following disciplines participate in the follow-up program: a pediatric surgeon, pediatricians, developmental psychologists, ICU nurses, a social worker, a clinical geneticist and pediatric physiotherapists. Children and their parents are evaluated when the child is 6, 12, and 24 months and 5, 8, 12 and 16 - 18 years of age. Recently, reports became available on growth and development within the first 24 months in children with CA and on a nationwide evaluation of 5-year olds following neonatal ECMO treatment.[22,23] CA survivors showed impaired growth and psychomotor developmental delay up to age 2 years, and ECMO treated neonates presented with considerable morbidity at age 5 years. These findings warrant a dedicated multidisciplinary follow-up team evaluating morbidity up till adolescence.

Pediatric physical therapy



The pediatric physical therapist has an important role in the follow-up program evaluating the children's motor development and exercise capacity at different ages. Standardized measurement instruments are used for this aim. Motor development is measured with the Movement Assessment Battery for Children (MABC).[24,25] Exercise capacity in children aged 5 to 13 years is measured with the Bruce treadmill protocol.[26] At later age an electrically braked cycle is used with progressively increasing workload reaching maximum tolerance in about 10 min.

In a previous study we used reference data by Cumming and colleagues to evaluate exercise capacity in 29 five-year-olds following neonatal ECMO treatment.[23,27] Compared with these reference data abnormal or suspect decreased exercise capacity was observed in 31% of children. We chose these reference data from American children published in 1978 despite the fact that more recent Dutch reference values from Binkhorst and colleagues were available.[28] The latter, however, were obtained in a small sample of children in the age range between 4 - 6 years. Should we have used the Dutch reference values, 41% of the children would have scored below the 5th percentile.

Nevertheless, we wondered whether the low exercise capacity could be explained by a real impaired physical condition following neonatal ECMO or by the lack of adequate reference data representative of the exercise capacity of contemporary healthy Dutch children. Considering that children's exercise capacity may have deteriorated during the past decades – due to decreased physical activity levels and more calory-rich foods – we felt that an update of the Dutch reference values was much needed.

AIMS OF THE RESEARCH AND STRUCTURE OF THIS THESIS

Bruce treadmill protocol

In line with the above considerations our first aim was to establish new reference values for exercise capacity using the Bruce treadmill protocol in children aged 4 - 13 years. To test the hypothesis that exercise capacity had deteriorated over time we also set out to compare our new reference values with those of Binkhorst et al.[28] A secondary aim was to evaluate possible determinants of exercise capacity: height for age, body mass index (BMI), smoking habits, ethnicity, socioeconomic status (SES), sports participation, and school transport habits. The Bruce treadmill protocol has rather large increments in workload between stages. It is therefore that in the Netherlands many pediatric physical therapists use the so-called 'half-Bruce' treadmill protocol for young children. However, the results of the original and half-protocol have never been compared. We assumed that, because of the difference in workload between the two protocols, children's maximal endurance times using the 'half-Bruce' treadmill protocol would be lower than those for the original protocol. Therefore, we compared the endurance times on the treadmill using the original Bruce protocol and the 'half-Bruce' protocol in children aged 4 and 5 years. We aimed to introduce the newly established reference values for the Bruce treadmill protocol in future evaluation of exercise capacity in our follow-up program.

Anatomical congenital anomalies

We hypothesized that patients suffering from CA associated with abnormal lung development are at risk for long-term respiratory morbidity, including delayed motor function development and reduced exercise capacity. Therefore, we evaluated respiratory morbidity, motor function development and exercise capacity in 5-year-old children with CDH and EA. To evaluate the long-term sequelae of abnormal lung development on exercise capacity we evaluated exercise capacity and daily activities in a cohort of young adult CDH survivors and in matched controls.

Extracorporeal Membrane Oxygenation

Because ECMO is used in neonates with severe respiratory insufficiency when conventional management fails, we assumed that this group of patients is at risk for respiratory morbidity including motor function problems and reduced exercise capacity. The first studies confirmed this hypothesis.[23,29,30] Therefore, we aimed to evaluate in more detail the characteristics and possible determinants of motor performance at five years of age following neonatal ECMO. In addition we analysed longitudinal data on exercise capacity in ECMO survivors between 5 and 12 years of age. Different subgroups were analysed to test the hypothesis that children with abnormal lung development are more prone to decreased exercise capacity at older age.

Structure of this thesis

In Chapters 1 and 2 we describe the studies aimed at obtaining new reference values for the Bruce treadmill protocol.

Chapters 3 to 5 highlight the exercise capacity and motor development of survivors born with major anatomical anomalies.

Chapters 6 and 7 evaluate motor development and exercise capacity after neonatal ECMO.

The main findings and conclusions of this thesis are addressed in the general discussion. Finally, recommendations for further research and follow-up are given.

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PART I

REFERENCE VALUES BRUCE PROTOCOL

Chapter 1
Exercise capacity in Dutch children;
new reference values for the Bruce treadmill protocol
Monique H.M. van der Cammen-van Zijp, Rita J.G. van den Berg-Emons,
Sten P. Willemsen, Henk J. Stam, Dick Tibboel, Hanneke IJsselstijn.
Scandinavian Journal of Medicine & Science in Sports, 2010;20:e130-e136.

Chapter 2
Exercise testing of pre-school children using the Bruce treadmill protocol;
new reference values
Monique H.M. van der Cammen-van Zijp, Hanneke IJsselstijn, Tim Takken,
Sten P. Willemsen, Dick Tibboel, Henk J. Stam, Rita J.G. van den Berg-Emons.
European Journal of Applied Physiology, 2010;108:393-399.

Chapter 1

Exercise capacity in Dutch children;
new reference values for the Bruce treadmill protocol

ABSTRACT

The Bruce treadmill protocol is suitable for children 4 years of age and older. Dutch reference values were established in 1987. We considered that children's exercise capacity has deteriorated due to changes in physical activity patterns and eating habits. We determined new reference values and evaluated determinants of exercise capacity. Healthy Dutch children (n = 267) aged 6 - 13 years participated in this cross-sectional observational study. The maximal endurance time on the treadmill was the criterion of exercise capacity. Furthermore, we obtained data on anthropometry, smoking habits, socioeconomic status, ethnicity, sports participation, and school transport habits. The maximal endurance time for children aged up till 10 was lower (up to 1.6 and 1.4 min in girls and boys, respectively) than previously published. Body mass index was negatively, and intense sports participation was positively associated with endurance time (β = -0.412 and 0.789, respectively; $p < 0.001$). In conclusion, exercise capacity seems to have deteriorated in Dutch children aged up till 10 years whereas the values from the older children are remarkably similar to those from the previous study.

INTRODUCTION

Exercise testing provides information on exercise capacity and facilitates assessment of pathophysiologic characteristics, effectiveness of medication, and risk of potential disease.[1] Because children have relatively undeveloped knee extensors, treadmill testing is preferred over cycle ergometry especially for those lower than 8 years of age.[1] The Bruce treadmill protocol is well fitted for children 4 years of age onwards[2] and is preferred to cycle ergometry for clinical exercise testing in children in the United States.[3] In the Netherlands, the Bruce treadmill protocol is used not only in clinical settings but also by local pediatric physical therapists.

Dutch reference values for the Bruce treadmill protocol were established in 1987.[4] It may be doubted, whether these values reflect contemporary exercise capacity of healthy Dutch children. We hypothesized that exercise capacity has deteriorated. This hypothesis is supported by Chatrath for urban American children: children in 2002 showed a shorter endurance time on the Bruce treadmill test than children tested in 1977.[5,6] They reported a strong inverse relationship between body mass index (BMI) and endurance time. A similar trend was observed in Danish children between 1985 - 1986 and 1997 - 1998.[7] In view of this hypothesis we set out to: (1) determine new reference values for exercise capacity as indicated with the Bruce treadmill test for healthy Dutch children; (2) compare these new reference values with the previously established reference values by Binkhorst et al.[4] and (3) evaluate height for age, BMI, smoking habits, ethnicity, socioeconomic status (SES), sports participation, and school transport habits as possible determinants of exercise capacity.

PARTICIPANTS AND METHODS

We recruited healthy children, aged 6 - 13 years, attending five primary and secondary schools in the Southwestern part of the Netherlands. The schools were located in both urban and suburban regions. Teachers distributed 455 information letters and pre-test questionnaires to their pupils.

Exclusion criteria were: impaired motor development, use of medication affecting exercise capacity, or pulmonary and cardiovascular disease. Furthermore, we excluded obese children [weight for height ratio above +2 standard deviation scores (SDS)[8]] from analysis. We aimed at studying 30 boys and 30 girls for each age band of 2 years.

Study design

We performed this cross-sectional observational study between July 2006 and January 2007. The children were tested in a quiet room at their own schools. A minority of children performed the test in the hospital's exercise room. Parents of all participants

filled out a pre-test questionnaire. Parental estimation of their child's fitness level was classified as higher than, equal to or less than that for children of the same age.

The Erasmus MC Medical Ethical Review Board approved the study and we obtained written informed consent from all parents or guardians and for children aged 12 and 13 years also from the children.

The Bruce treadmill test

A motor-driven treadmill (En Mill, Enraf Nonius, Rotterdam, the Netherlands) was programmed for increases in angle of inclination and speed according to Bruce et al.[2] (Table 1). The children were permitted to hold on to the guardrail for maximally 5 seconds only to regain balance during changes of speed and angle of inclination. A physical therapist trained to apply Basic Life Support to children supervised all tests. We encouraged the children to perform to voluntary exhaustion. Thereafter the children continued walking at a slope of 0% and a speed of 2 km/h for 2 min. The maximal endurance time (in minutes, one decimal) served as criterion of exercise capacity. Before and during the test we monitored heart rate and transcutaneous oxygen saturation with a pulse Oximeter (MARS, motion artifact reduction system, type 2001, Respironics Novametrix, Murrysville, PA, USA). Heart rate of ≥ 185 beats per min (bpm)[9] or loss of coordination was considered to indicate maximal performance.

Determinants of exercise capacity

Pre-test questionnaire

The parental pre-test questionnaire included questions on means of school transport habits, one-way travel distance, sports participation, active and passive smoking, ethnic origin, and SES. Sports participation was classified into low (only school gymnastic lessons), moderate (gymnastic lessons and participation in organized sports up to 2 hours weekly) or high (gymnastic lessons and more than 2 hours of organized sports weekly). We classified ethnic origin using the definition of Statistics Netherlands into "Dutch", "Western background" or "non-Western background".[10] We assessed SES by questions about employment and education of both parents. SES was classified into: "low", "middle", and "high".[11] For children who cycled to school a weekly commuting distance (in km) was calculated by multiplying the one-way travel distance by 10.

Pre-test evaluation

A pre-test evaluation included measurement of height (cm) and weight (kg) using a stadiometer (Seca 206, Seca, Hamburg, Germany) and a scale (Beurer PS-16, Beurer, Ulm, Germany), respectively. The Dutch Growth Analyser, version 3.0 (Dutch Growth Foundation, Rotterdam, the Netherlands) served to calculate SDS for height, BMI, and weight for height on the basis of Dutch reference values published in 2000.[8]

Table 1 *Bruce treadmill protocol*

	Bruce		
Stage	Speed (km/h)	Grade (%)	Time (min)
I	2.7	10	3
II	4	12	3
III	5.4	14	3
IV	6.7	16	3
V	8	18	3
VI	8.8	20	3
VII	9.6	22	3

DATA ANALYSES

Data are presented for boys and girls separately. We performed a construction of age-related reference centiles according to Altman.[12] In brief: the endurance time is assumed to follow a normal distribution for a given age and sex. First the mean endurance time is modelled as a function of age. The absolute residuals of this regression are then regressed on age to provide an estimate of the standard deviation (SD) of the endurance time as a function of age. Means and SDs were combined to provide estimates for the centiles (centile = mean + Z x SD where Z is the corresponding centile of the standard normal distribution). We used a restricted cubic spline (with knots at the age of 7, 10, and 13) to obtain flexibility in the functional form of the relation of mean endurance time.[13] The SD was modelled using a linear model. When the slope of this model was not significant the SD was assumed to be constant.

Furthermore, we investigated whether differences in SDS endurance time could be explained by SDS height for age, SDS BMI, sports participation, school transport habits, smoking habits, ethnicity, or SES. We used linear regression analyses with the SDS of the endurance time as outcome variable in order to detect relevant determinants (i.e. bivariate significant) to include in multiple regression models. We present the regression coefficients (β) and explained variance (R^2) of the linear regression models.

Group comparisons (differences in the subject characteristics between boys and girls) were performed with the independent t-test, Mann-Whitney U test or Chi-square test where appropriate. Correlation coefficients between estimated levels of fitness and SDS of the endurance times were established with the Spearman's correlation test. Data presented are mean ± SD, unless stated otherwise. Statistical significance is accepted at a 1% level for all tests. Statistical analyses were performed using SPSS 14.0 for Windows.

Table 2 *Subject characteristics*

	Total	**Boys**	**Girls**
	n = 267	n = 133	n = 134
Height SD-scores, mean (SD)	0.17 (1.00)*	0.23 (0.83)	0.12 (1.12)†
Weight-for-height SD-scores, mean (SD)	0.01 (1.00)	0.06 (0.98)	-0.025 (1.04)
BMI SD-scores, mean (SD)	0.06 (1.00)	0.11 (0.98)	-0.003 (1.02)
Passive smoking, n (%)	34 (12.7)	16 (12.0)	18 (13.5)
SES			
high, n (%)	182 (68.2)	97 (73.0)	85 (63.4)
middle, n (%)	62 (23.2)	24 (18.0)	38 (28.4)
low, n (%)	22 (8.2)	12 (9.0)	10 (7.4)
missing, n (%)	1 (0.4)	--	1 (0.8)
Ethnic group			
Dutch, n (%)	222 (83.2)	118 (88.7)	104 (77.6)
Western background, n (%)	23 (8.6)	7 (5.3)	16 (11.9)
Non-Western background, n (%)	22 (8.2)	8 (6.0)	14 (10.5)
Sports participation			
high, n (%)	131 (49.1)	78 (59.6)	53 (39.6)
moderate, n (%)	100 (37.4)	35 (26.3)	65 (48.5)
low, n (%)	35 (13.1)	20 (15.1)	15 (11.2)
missing, n (%)	1 (0.4)	--	1 (0.7)
Home/school commuting			
by car or sitting at parent's bicycle, n (%)	37 (13.9)	20 (15.0)	17 (12.7)
walking or public transport, n (%)	80 (30.0)	40 (30.1)	40 (29.9)
cycling, n (%)	150 (56.1)	73 (54.9)	77 (57.4)
Parental estimation of fitness level			
better than peers, n (%)	44 (16.5)	24 (18.1)	20 (14.9)
similar to peers, n (%)	209 (78.3)	103 (77.4)	106 (79.1)
worse than peers, n (%)	10 (3.7)	4 (3.0)	6 (4.5)
missing, n (%)	4 (1.5)	2 (1.5)	2 (1.5)

Independent t-test
* *significantly different from zero: p = 0.005,*
† *significantly different from zero: p = 0.002*

RESULTS

Three hundred thirty-two of the 455 invited children (73%) were willing to participate; 114 parents did not respond and nine refused to participate. Nine of these 332 children were not tested for medical reasons: six had pulmonary or cardiovascular disease, two had a broken arm, and one child underwent chemotherapy. Thirty-nine children were

not tested for organizational reasons. Furthermore, 17 children (5%) were excluded from analysis because of obesity (n = 3), no maximal exercise performed (n = 2), muscular problems (n = 2), and inability to walk without holding the guardrail (n = 9). Thus, final analysis was on 267 children (59%; Table 2). There were no significant differences between boys and girls in any of the characteristics. None of the children reported to smoke.

Reference values for exercise capacity

Percentile scores for exercise capacity for the children are shown in Tables 3 and 4 for boys and girls, respectively. The age-related reference centiles are graphically shown in Figure 1 (a and b).

Heart rate at maximal performance reliably recorded for 185 children (69%) was a mean of 197 ± 8 bpm. Technical problems precluded reliably recording for the other 82 children. Still, for 74 of these children a heart rate of ≥ 185 bpm had been recorded just before maximal exercise. For none of the children the transcutaneous oxygen saturation was ≤ 94%. We found positive correlations between the estimated levels of exercise capacity and the endurance SD-scores (r_s = 0.4, p < 0.001).

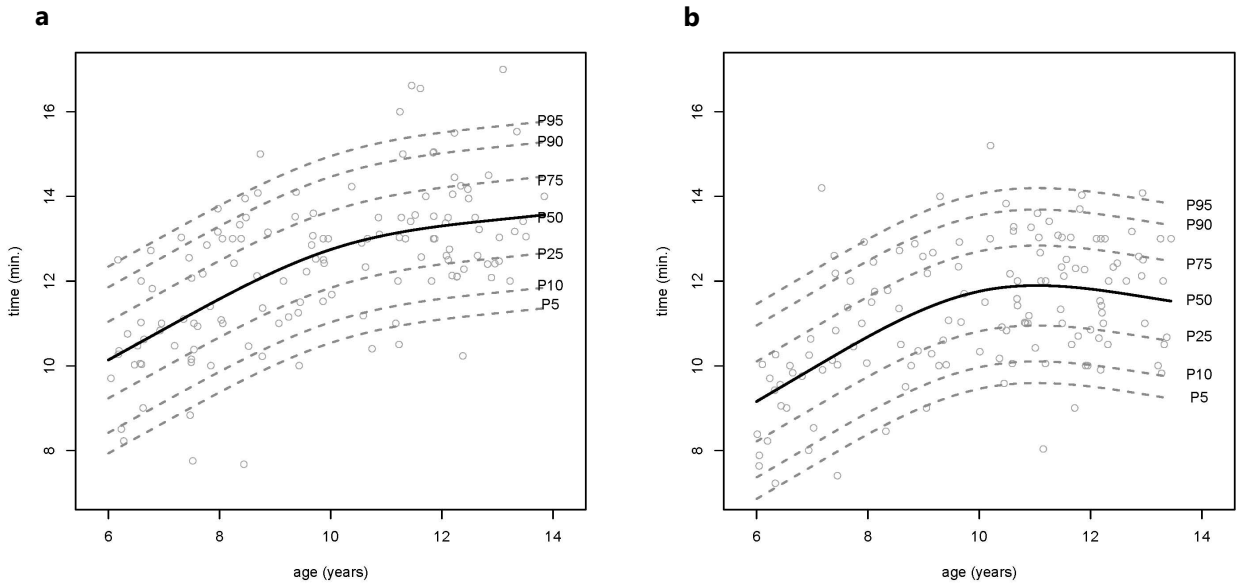

Figure 1 (a and b) *Maximal endurance time on the Bruce treadmill test for boys (a) and girls (b) (selected centiles). The open circles represent each individual subject*

Table 3 *Maximal endurance time in minutes for boys: centiles*

Age (yrs)	p 5	p 10	p 25	p 50	p 75	p 90	p 95	Maximum HR*
6.0	7.9	8.4	9.2	10.1	11.0	11.9	12.3	194 ± 11
6.5	8.3	8.8	9.6	10.5	11.4	12.2	12.7	202 ± 8
7.0	8.7	9.1	10.0	10.9	11.8	12.6	13.1	191 ± 9
7.5	9.0	9.5	10.3	11.2	12.1	12.9	13.4	197 ± 6
8.0	9.4	9.9	10.7	11.6	12.5	13.3	13.8	198 ± 14
8.5	9.7	10.2	11.0	11.9	12.8	13.6	14.1	188 ± 0
9.0	10.0	10.5	11.3	12.2	13.1	14.0	14.4	198 ± 9
9.5	10.3	10.8	11.6	12.5	13.4	14.2	14.7	194 ± 0
10.0	10.5	11.0	11.8	12.8	13.7	14.5	15.0	199 ± 8
10.5	10.7	11.2	12.0	12.9	13.8	14.7	15.2	193 ± 7
11.0	10.9	11.4	12.2	13.1	14.0	14.8	15.3	199 ± 10
11.5	11.0	11.5	12.3	13.2	14.1	14.9	15.4	201 ± 11
12.0	11.1	11.6	12.4	13.3	14.2	15.0	15.5	199 ± 6
12.5	11.2	11.7	12.5	13.4	14.3	15.1	15.6	192 ± 15
13.0	11.2	11.7	12.6	13.5	14.4	15.2	15.7	197 ± 5

* *Maximum heart rate in bpm; mean ± 1 standard deviation (SD).*
Total n = 133; ages 6 and 7 years: n = 37; 8 and 9 years: n = 35; 10 and 11 years: n = 29; 12 and 13 years: n = 32. SD endurance time = 1.3 min

Table 4 *Maximal endurance time in minutes for girls: centiles*

Age (yrs)	p 5	p 10	p 25	p 50	p 75	p 90	p 95	Maximum HR*
6.0	6.9	7.4	8.2	9.2	10.1	11.0	11.5	195 ± 9
6.5	7.2	7.8	8.6	9.5	10.5	11.3	11.9	195 ± 5
7.0	7.6	8.1	9.0	9.9	10.9	11.7	12.2	191 ± 9
7.5	8.0	8.5	9.4	10.3	11.3	12.1	12.6	190 ± 12
8.0	8.4	8.9	9.7	10.7	11.6	12.5	13.0	195 ± 6
8.5	8.7	9.2	10.1	11.0	12.0	12.8	13.3	197 ± 7
9.0	9.0	9.5	10.4	11.3	12.3	13.1	13.6	201 ± 1
9.5	9.3	9.8	10.6	11.6	12.5	13.4	13.9	200 ± 13
10.0	9.5	10.0	10.8	11.8	12.7	13.6	14.1	202 ± 7
10.5	9.6	10.1	10.9	11.9	12.8	13.7	14.2	198 ± 7
11.0	9.6	10.1	10.9	11.9	12.8	13.7	14.2	201 ± 9
11.5	9.6	10.1	10.9	11.9	12.8	13.7	14.2	201 ± 6
12.0	9.5	10.0	10.9	11.8	12.8	13.6	14.1	202 ± 7
12.5	9.4	9.9	10.8	11.7	12.7	13.5	14.0	197 ± 8
13.0	9.3	9.8	10.7	11.6	12.6	13.4	13.9	197 ± 10

* *Maximum heart rate bpm; mean ± 1 standard deviation (SD)*
Total n = 134; ages 6 and 7 years: n = 33; 8 and 9 years: n = 26; 10 and 11 years: n = 48; 12 and 13 years: n = 27. SD endurance time = 1.4 min

Comparison with previously established Dutch reference values

Figure 2 shows the p 50-centiles from our study plotted against values presented by Binkhorst et al.[4] Values for children up to the age of 9 and 10 years (girls and boys respectively) in the present study are lower than the historical values (up to 1.6 and 1.4 min in girls and boys, respectively). The difference was most striking in the youngest children. As Binkhorst et al. did not provide exact sample sizes for each age and gender band we present the comparison graphically.

Determinants of exercise capacity

Linear regression showed that SDS BMI, SES, and sports participation were related to endurance SDS (Table 5). Multiple regression showed that 27% of the variance in endurance SDS was explained by SDS BMI, SES, and sports participation. Intense sports participation and SDS BMI were best predictive. Furthermore we explored possible relations between age and BMI or sports participation. BMI scores did not correlate with age. Intensity of sports participation correlated positively with age (r_s = 0.24; p < 0.001).

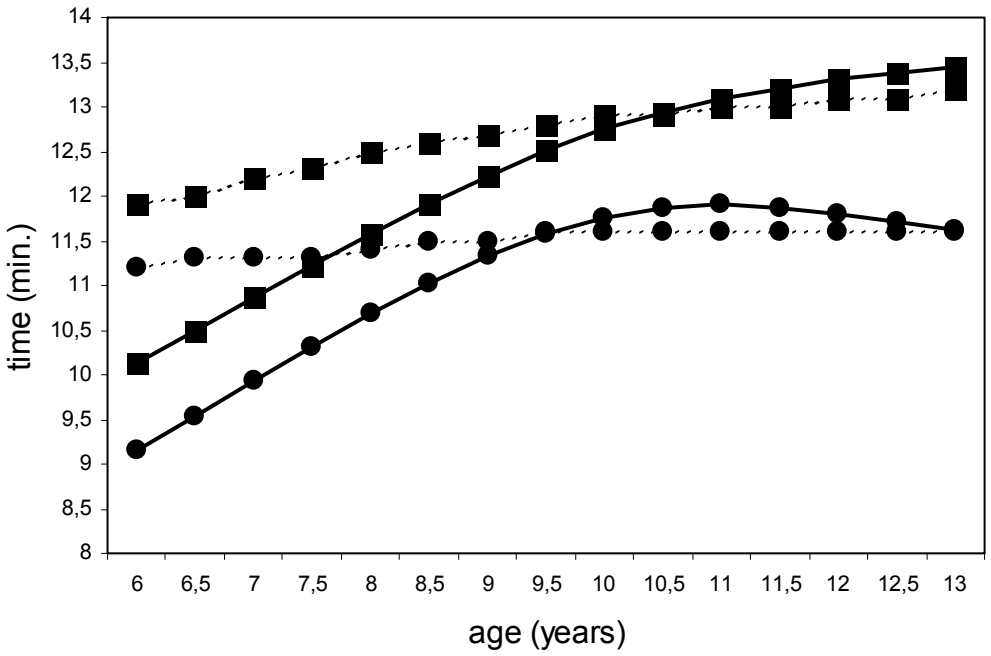

Figure 2 *Bruce protocol; endurance times in the current study (solid lines) and in the study of Binkhorst et al.[4] (dashed lines). Data from 6 to 13 years old boys (squares) and girls (circles) are shown*

Table 5 *Regression models for determinants affecting exercise capacity*

Independent variables	**SDS endurance time**		
	β	**p-value**	**R^2**
SDS BMI	-0.384	< 0.001*	0.143
SDS height for age	-0.023	0.713	0.001
Passive smoking	-0.433	0.019	0.020
SES		0.009*	0.035
SES (difference 0 and 1)	-0.011	0.963	
SES (difference 0 and 2)	0.399	0.077	
Ethnicity		0.337	0.008
Ethnicity (difference 0 and 1)	-0.175	0.430	
Ethnicity (difference 0 and 2)	-0.298	0.189	
Sports participation		< 0.001*	0.085
Sports participation (difference 0 and 1)	0.033	0.864	
Sports participation (difference 0 and 2)	0.613	0.001*	
Home/school commuting		0.081	0.019
Home/school (difference 0 and 1)	0.451	0.025	
Home/school (difference 0 and 2)	0.311	0.093	
Multiple			
SDS BMI, SES, Sports participation		< 0.001*	0.268
SDS BMI	-0.412	< 0.001*	
SES (difference 0 and 1)	-0.093	0.670	
SES (difference 0 and 2)	0.196	0.328	
Sports participation (difference 0 and 1)	0.220	0.207	
Sports participation (difference 0 and 2)	0.786	< 0.001*	

** = significant; SDS = standard deviation scores; β = regression coefficient; R^2 = explained variance; Passive smoking: no (0), yes (1); SES (socioeconomic status): low (0), middle (1), high (2); Ethnicity: Dutch (0), Western background (1) and non-Western background (2); Sports participation: low (0), middle (1), high (2); Home/school commuting: car or sitting at parent's bicycle (0), walking or public transport (1), cycling themselves (2)*

DISCUSSION

The present study provides an update of children's reference values for the Bruce exercise test. An update was felt necessary as the presently used values date from 1987 and children's activity levels are thought to have dropped. Endurance times for children up to the age of 9 and 10 years (girls and boys, respectively) in the present study were indeed lower than those for the children studied in 1987.[4] However, the values from the older children were remarkably similar to those from the previous study. BMI was

negatively associated, and intense sports participation was positively associated with maximal endurance time.

The sample of 267 healthy children was representative of the Dutch population with respect to ethnicity.[14] The sample included 59% of all invited children. Since background data on non-participants are lacking, some selection bias cannot be ruled out. Nevertheless, as the large majority of parents estimated their child's fitness level similar to that of age peers, a selection bias towards high fitness levels seems unlikely. Furthermore, a relatively large proportion of the sample was classified as high SES. Because we found a rather low but positive interaction between SES and SDS endurance time, we assume that children with lower SES may perform slightly worse. This would suggest that inclusion of more children from low SES families would have resulted in lower exercise capacity.

Although children in the study of Binkhorst et al.[4] were tested under slightly different conditions, we do not expect the differences between the study conditions to interfere with the main conclusion of our study. For example, children in the study of Binkhorst et al. had been given the opportunity to practice walking on the treadmill. We did not arrange opportunity to practice, because the Bruce protocol starts with walking for 3 min at a low speed, which provides for warming up and getting used to the treadmill. Furthermore, we also did not measure gas exchange parameters. Firstly, wearing a mask may lead to loss of cooperation and to submaximal results, especially in the younger children. Secondly, Cumming et al.[5] reported a strong correlation between the maximal endurance time and maximal oxygen uptake. They concluded that maximal endurance time might be used as a sole criterion of exercise capacity. We selected the present study design because our study conditions are in accordance with the everyday practice applied by pediatric physical therapists.

Two studies in North-American children and one in Italian children and adolescents report on exercise testing by the Bruce protocol in large samples as well (Table 6).[5,6,15] We found lower maximal endurance times, especially in the younger children, than did Cumming et al.,[5] and Maffulli et al.[15] Also Wedderkopp et al.[7] and Tomkinson and Olds[16] suggested this secular trend in exercise capacity in children.

We assume that both increased obesity and lower level of physical activity may explain the deterioration in exercise capacity.[17-19] In the Netherlands, children up to 7 years of age spend more time watching television than 5 years earlier and 2% of all children aged 3 years and over never play outdoors.[20] More and more children in the United Kingdom and Australia are being taken to school by car[21,22] and we assume that this holds true for the Netherlands as well. On the other hand, Metcalf found that the school run does not affect overall physical activity of 5-year-olds.[21]

Table 6 *Comparison of our results with previously published data on the Bruce treadmill protocol in children*

Age groups (years)	Binkhorst[4]	Cumming[5]	Maffulli[15]	Chatrath[6]	Current study
	n = 336*	n = 177	n = 160	n = 236	n = 267
Boys					
6 - 7	12.1 ± 1.5	11.8 ± 1.6	14.0 ± 1.8	9.6 ± 2.3	10.7 ± 1.3
8 - 9	12.7 ± 1.5	12.6 ± 2.3	15.2 ± 1.3	10.2 ± 2.5	12.1 ± 1.3
10 - 11	13.0 ± 1.5	12.7 ± 1.9†	15.4 ± 2.5	10.7 ± 2.1†	13.0 ± 1.3
12 - 13	13.2 ± 1.5		17.1 ± 2.2		13.4 ± 1.3
Girls					
6 - 7	11.3 ± 1.1	11.2 ± 1.5	12.7 ± 1.6	8.7 ± 2.0	9.7 ± 1.4
8 - 9	11.6 ± 1.1	11.8 ± 1.6	13.6 ± 2.3	9.8 ± 1.6	11.2 ± 1.4
10 - 11	11.6 ± 1.1	12.3 ± 1.4†	14.8 ± 1.2	10.2 ± 1.9†	11.8 ± 1.4
12 - 13	11.6 ± 1.1		14.0 ± 2.7		11.7 ± 1.4

Mean (± 1 SD) endurance time (min)
* *336 is the total study population (4 - 18-year-olds), the number of 6 - 13-year-olds is unclear.*
† *age group 10 - 12 years*

The cross-sectional design of our study does not allow to establish causal relations explaining the deteriorated exercise capacity in the youngest children. Attempts can be made to reverse the downward trend, but even individual life style recommendations have met with little success. It would seem therefore, that the best approach is creating better opportunities for children to be physically active in their daily environments (e.g. schools, roads, sports), stimulated by policy changes that aim at better eating habits.

Exercise capacity for older children does not seem to have changed, probably as a result of increasing sports participation during the past years and stabilization of time spent watching television.[20,23] Furthermore, members of sports clubs are the most likely to play outdoors.[20] In our study, the travel distance by bicycle correlated positively with age. Thus, older children seem to exert more physical exercise during home/school commuting.

Children from a large U.S. metropolitan area referred to a pediatric cardiology clinic but proven to be without cardiac abnormalities[6] performed worse than the children in our study. This may be explained by the inclusion of obese children in their sample (15% of the children had a BMI > 95th percentile). In our study, the three children with obesity were excluded from analysis.

Children in our study were permitted to hold on to the guardrail for maximally 5 seconds only to regain balance during changes of speed and angle of inclination. We refrained from using a harness because in the Bruce protocol the belt speed is slow and using a harness may lead to loss of cooperation and to submaximal results. Nine of the 6-year-olds (eight girls and one boy) were not able to perform without holding the guardrails and reached longer endurance time than did their age peers. For the eight girls this was 10.7 against 9.2 min ($p = 0.003$). This finding confirms that holding the guardrail adds to the endurance time.[5] Thus, the reference values established in the current study are only applicable for children who are able to walk without holding the guardrail, apart from brief moments to regain balance during changes of speed and angle of inclination.

PERSPECTIVES

Our hypothesis that exercise capacity might have deteriorated over the years was confirmed for children aged 6 - 10 years. We assume that a change in lifestyle with younger children spending more leisure time playing computer games and/or watching television may be important.[17,19,20] For older children exercise capacity does not seem to have changed over the years probably as a result of increasing sports participation and stabilization of time spent watching television[20,23] (Figure 2). Younger children (up from the age of 4 years) are assumed to be able to perform the Bruce treadmill test too, but may need a slight modification of the protocol, i.e. holding the rail. Since intense sports participation interacts positively and BMI interacts negatively with exercise capacity, recommendations targeted at improvement of daily environment and a healthy eating pattern may be important to improve children's exercise capacity.

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Chapter 2

Exercise testing of pre-school children using the Bruce treadmill protocol; new reference values

ABSTRACT

The Bruce treadmill protocol is an often-used exercise test for children and adults. Few and mainly old normative data are available for young children. In this cross-sectional observational study we determined new reference values for the original Bruce protocol in children aged 4 and 5 years. Furthermore, we compared the original protocol with the so-called 'half-Bruce' protocol. In the Netherlands this half-Bruce protocol is often used for young children because of the rather large increments in workload in the original protocol. Seventy-eight healthy Dutch children participated. The maximal endurance time was the criterion of exercise capacity. The new reference values for the original Bruce protocol are presented as reference centiles. The mean (SD) endurance time using the original protocol was 10.2 (SD 1.5) min; this was 9.4 (1.3) min for the half-Bruce protocol. The mean difference was 50 seconds (95% CI: 29 - 71 s, $p < 0.001$). So, for children aged 4 and 5 years the endurance times obtained with the original and half-Bruce protocol are different and should not be considered interchangeable. Our new reference values can be used as reference values for the original Bruce protocol.

INTRODUCTION

Exercise testing provides information on exercise capacity and facilitates assessment of pathophysiologic characteristics, effectiveness of medication, and risk of potential disease.[1] Since children have relatively undeveloped knee extensors, treadmill testing is preferred over cycle ergometry in young children.[1,2] An often used protocol is the Bruce treadmill protocol, which was originally designed for adults[3] but is now also applied worldwide for children from the age of 4 years.[4]

Reference values for children aged 4 and 5 years have been established mainly in small study samples.[4-6] Only Cumming et al.[7] presented values obtained in a larger group (up to forty 4 - 5 years olds). However, these data date back more than 30 years and might therefore not be appropriate for contemporary children.[4] Recently, we showed that the maximal exercise capacity in children from 6 to 10 years seems to have deteriorated during the past 20 years. In these children, body mass index (BMI) was negatively, and intense sports participation was positively associated with endurance time.[8]

The original Bruce treadmill protocol has rather large increments in workload between stages. It is therefore that in the Netherlands many pediatric physical therapists use the so-called 'half-Bruce' treadmill protocol for young children. This modified protocol has 1.5 min stages instead of 3 min stages and smaller speed increments (Table 1). As reference values for the modified protocol are lacking, those for the original Bruce protocol are then applied.[9] We hypothesize, however, that because of the difference in workload, children's maximal endurance times using this half-Bruce treadmill protocol are lower than those for the original Bruce protocol.

In view of these observations, the primary objective of the present study was to determine reference values for healthy Dutch children aged 4 and 5 years using the original Bruce treadmill protocol. The secondary objectives were: (1) to compare the endurance times on the original and half-Bruce protocol; (2) to evaluate BMI, height for age, socioeconomic status (SES), ethnicity, sports participation, and school transport habits as possible determinants of exercise capacity.

SUBJECTS AND METHODS

We recruited 80 healthy children aged 4 - 5 years (39 boys and 41 girls) from three different primary schools in the Southwestern part of the Netherlands. The schools were located in both urban and suburban regions. Children were considered to be healthy when parents declared that their child did not suffer from pulmonary or cardiovascular disease or a health condition treated by a medical specialist. We excluded children with impaired motor function; children who used medication affecting exercise capacity; and obese

children [BMI above +2 standard deviation scores (SDS) compared to Dutch norms].[10] Also excluded from analysis were children who did not fulfill the criteria of maximal exercise performance as described below. As two children were excluded, one for cardiovascular disease and one due to sub maximal performance, 78 children were evaluated.

Study design

This cross-sectional observational study was performed between July 2006 and March 2008. We used two different study designs: (1) To compare the original Bruce protocol with the half-Bruce protocol 53 children were randomly allocated to start with one of the two exercise test protocols (Figure 1; Group I). They performed both test protocols within a period of 1 - 14 days. (2) To obtain reference values for the original Bruce protocol, we studied 53 children who performed the Bruce treadmill protocol without prior experience on exercise testing (Figure 1; Group II).

Most children were tested in a quiet room at their own schools. Some, living close by, performed the test in the hospital's exercise room. In accordance with daily practice and the procedure applied in former research, they were not given the opportunity to practise. Parents of all participants filled out a pre-test questionnaire as established previously.[8] Parental estimation of their child's fitness level was classified as higher than, equal to or less than that for children of the same age.

The Erasmus MC Medical Ethical Review Board approved the study. Written informed consent was obtained from all parents or guardians.

Table 1 *Test details for the Bruce and the half-Bruce treadmill protocol*

Bruce				**Half-Bruce**			
stage	speed (km/h)	grade (%)	time (min)	stage	speed (km/h)	grade (%)	time (min)
I	2.7	10	3	I	2.7	10	1.5
				II	3.4	11	1.5
II	4	12	3	III	4	12	1.5
				IV	4.7	13	1.5
III	5.4	14	3	V	5.4	14	1.5
				VI	6	15	1.5
IV	6.7	16	3	VII	6.7	16	1.5
				VIII	7.3	17	1.5
V	8	18	3	IX	8	18	1.5
				X	8.4	19	1.5
VI	8.8	20	3	XI	8.8	20	1.5
				XII	9.2	21	1.5

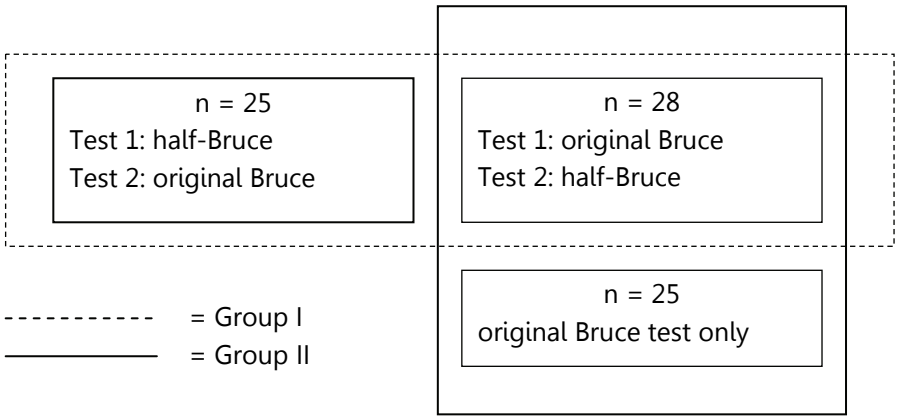

Figure 1 *Number of participants studied for each protocol. The square with dashed lines indicates the 53 subjects, who were tested twice in order to evaluate the difference between the original and the 'half-Bruce' (Group I). The square with solid lines indicates the 53 subjects, who were included in the determination of reference values (Group II): those who were tested twice and started with the original protocol (n = 28) and those who were only tested once (n = 25)*

The treadmill tests

The children performed the maximal exercise tests on a motor-driven treadmill (En Mill, Enraf Nonius BV, Rotterdam, The Netherlands) programmed for increases in angle of inclination and speed for the original Bruce protocol or for the half-Bruce protocol, as applicable (Table 1).

A physical therapist trained to apply Basic Life Support to children supervised all tests. In view of the children's young age, we slightly modified the procedure by permitting them to hold the guardrail to maintain body position near the center of the moving belt. From experience we knew that otherwise they would have balance problems. We encouraged the children to perform to voluntary exhaustion. Thereafter, the children continued walking at a slope of 0% and a speed of 2 km/h for 2 min. The maximal endurance time (in minutes, two decimals) served as criterion of exercise capacity. Before and during a test, heart rate (HR) was monitored with a pulse oximeter (MARS, motion artifact reduction system; type 2001, Respironics Novametrix, Murrysville, PA) attached to the index finger. HR of ≥ 185 beats per minute (bpm) at the end of the test[11] or loss of walking-coordination was considered to indicate maximal performance. If any technical problems precluded measurements at the end of the test, we considered maximal performance to be based on HR as monitored in the pre-final stage of the test.

Determinants of exercise capacity

Pre-test questionnaire

The parental pre-test questionnaire included questions on school transport habits, one-way travel distance, sports participation, passive smoking, ethnic origin, and SES. For children who cycled to school 5 days per week a weekly commuting distance (in km) was calculated by multiplying the one-way travel distance by 10. Sports participation

was classified into low (only school gymnastic lessons), moderate (gymnastic lessons and participation in organized sports up to 2 h weekly), or high (gymnastic lessons and more than 2 h of organized sports weekly). We classified ethnic origin using the definition of Statistics Netherlands into 'Dutch', 'Western background' or 'non-Western background'.[12] SES was classified into: 'low', 'middle', and 'high'.[13]

Pre-test evaluation

A pre-test evaluation included measurement of height (cm) and body mass (kg) using a stadiometer (Seca 206, Seca, Hamburg, Germany) and a scale (Beurer PS-16, Beurer, Ulm, Germany), respectively. The Dutch Growth Analyser, version 3.0 (Dutch Growth Foundation, Rotterdam) served to calculate SDS for height and BMI, on the basis of Dutch reference values published in 2000.[14]

DATA ANALYSIS

Data for children in Group II served to establish reference values for the original Bruce protocol. Age-related reference centiles were constructed according to Altman.[15] In brief, the endurance time is assumed to follow a normal distribution for a given age and sex. First, the mean endurance time is modeled as a function of age. The absolute residuals of this regression are then regressed on age to provide an estimate of the standard deviation of the endurance time as a function of age. Means and standard deviations were combined to give estimates for the centiles (centile = mean + Z x SD, where Z is the corresponding centile of the standard normal distribution).

One-sample t-tests were performed to analyze differences in anthropometric parameters between the norm group (Group II) and the general population norms.[14]

For participants in Group I we compared the effects of the two different Bruce protocols using ANOVA for repeated measurements.[16] We tested whether there was a learning effect; i.e., whether a subject after a first Bruce test – irrespective of what protocol – would score better on the second test than he or she would have done when performing this test without prior experience. Finally, we tested to see if there was a sequence by treatment interaction; i.e., whether the size of the learning effect depended on which form of the Bruce test was taken first. Group comparisons (differences in the subject characteristics between subgroups in Group I; Figure 1), were performed with the independent t-test, Mann-Whitney U test or Chi-square test where appropriate.

To evaluate determinants of exercise capacity corrected for sex and age we first calculated the SDS of the endurance time, i.e., the difference between the observed and predicted value divided by the standard deviation from the reference values. Then, we

investigated whether differences in endurance time in the children of group II, could be explained by SDS height, SDS BMI, SES, ethnicity, sports participation or school transport habits. We used linear regression analyses with the SDS of the maximal endurance time as outcome variable.

Paired-samples t-tests were used to evaluate the differences in HR during the original and half-Bruce protocol. P values < 0.01 were considered statistically significant. Data presented are mean (SD), unless stated otherwise. Statistical analyses were performed using SPSS 15.0 for Windows.

RESULTS

Reference values for exercise capacity

The characteristics of the children from the reference group (Group II) are shown in Table 2. None of the children were exposed to smoking. SDS height and BMI did not significantly differ from general population norms.

The percentile scores for endurance time are presented in Table 3. The age-related reference centiles are graphically shown in Figure 2 (a and b). A good fit could be achieved using a linear function for the mean. Variance did not depend on age, so we could use a constant variance. At the end of the test HR was reliably recorded in 36 children (70%). It was a mean of 191 bpm (SD 11) in boys and a mean of 195 bpm (SD 9) in girls, indicating maximal performance. Technical problems precluded reliable recording of HR in the final stage of the test for the other 17 children, but, based on HR in their pre-final stage or loss of coordination, we considered performance in those children also as maximal.

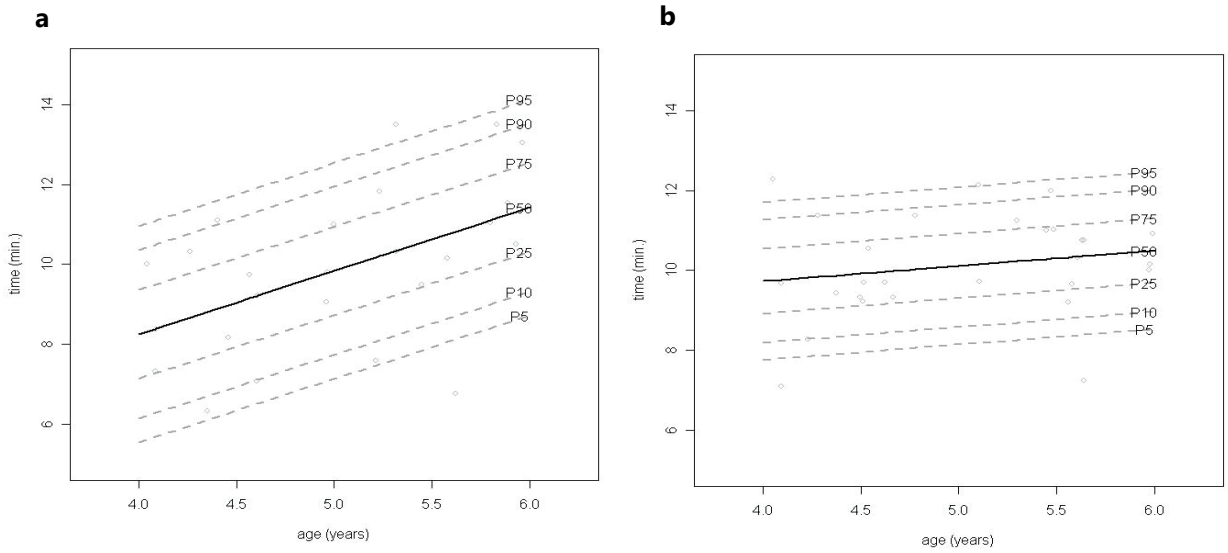

Figure 2 *Centile chart of endurance time in boys (a) and girls (b)*

Table 2 *Characteristics of participants for establishment of reference data (group II)*

	Boys	**Girls**	**Total**
	n = 25	n = 28	n = 53
Age in years, mean (SD)	5.0 (0.6)	5.0 (0.6)	5.0 (0.6)
Height SD-scores, mean (SD)	-0.26 (1.0)	0.42 (0.9)	0.09 (1.0)
BMI SD-scores, mean (SD)	0.24 (0.8)	0.16 (1.0)	0.20 (0.9)
Socioeconomic status (SES), n (%)			
High	17 (68.0)	22 (78.6)	39 (73.6)
Middle	8 (32.0)	5 (17.8)	13 (24.5)
Low	-	1 (3.6)	1 (1.9)
Ethnic group, n (%)			
Dutch	20 (80.0)	25 (89.3)	45 (84.9)
Western background	1 (4.0)	1 (3.6)	2 (3.8)
Non Western background	4 (16.0)	2 (7.1)	6 (11.3)
Sports participation, n (%)			
High	1 (4.0)	1 (3.6)	2 (3.8)
Moderate	18 (72.0)	19 (67.8)	37 (69.8)
Low	6 (24.0)	8 (28.6)	14 (26.4)
Home/school commuting, n (%)			
By car or sitting at parent's bicycle	6 (24.0)	9 (32.1)	15 (28.3)
Walking or public transport	13 (52.0)	7 (25.0)	20 (37.7)
Cycling themselves	6 (24.0)	11 (39.3)	17 (32.1)
Missing	-	1 (3.6)	1 (1.9)
Parental estimation of fitness level, n (%)			
Better than peers	4 (16.0)	1 (3.6)	5 (9.4)
Similar than peers	19 (76.0)	26 (92.8)	45 (84.9)
Worse than peers	1 (4.0)	1 (3.6)	2 (3.8)
Missing	1 (4.0)	-	1 (1.9)

Difference between the two protocols

Children in subgroups of Group I (Figure 1) did not differ with respect to age, anthropometric data, exposure to smoking, SES, ethnicity, sports participation, school transport habits, and parental estimation of fitness level (data not shown). The mean endurance time using the original Bruce protocol was 10.2 min (SD 1.5); that was 9.4 min (SD 1.3) for the half-Bruce protocol. The mean difference was 50 s (95% CI: 29 - 71 s; $p < 0.001$). We noted a significant learning effect of 47 s (95% CI: 26 - 68 s; $p < 0.001$). There was no significant interaction between sequence and the results of the Bruce tests ($p = 0.851$).

Table 3 *Endurance times for boys and girls*

Gender	Age (years)	p 5	p 10	p 25	p 50	p 75	p 90	p 95
Boys	4.00	5.55	6.14	7.14	8.25	9.36	10.36	10.96
	4.25	5.94	6.54	7.54	8.65	9.76	10.76	11.35
	4.50	6.34	6.94	7.94	9.05	10.16	11.15	11.75
	4.75	6.74	7.34	8.33	9.44	10.55	11.55	12.15
	5.00	7.14	7.73	8.73	9.84	10.95	11.95	12.55
	5.25	7.53	8.13	9.13	10.24	11.35	12.35	12.94
	5.50	7.93	8.53	9.53	10.64	11.74	12.74	13.34
	5.75	8.33	8.92	9.92	11.03	12.14	13.14	13.74
Girls	4.00	7.76	8.20	8.92	9.73	10.54	11.27	11.70
	4.25	7.86	8.29	9.02	9.83	10.64	11.36	11.80
	4.50	7.95	8.39	9.12	9.92	10.73	11.46	11.89
	4.75	8.05	8.48	9.21	10.02	10.83	11.55	11.99
	5.00	8.14	8.58	9.31	10.12	10.92	11.65	12.09
	5.25	8.24	8.68	9.40	10.21	11.02	11.75	12.18
	5.50	8.34	8.77	9.50	10.31	11.11	11.84	12.28
	5.75	8.43	8.87	9.59	10.40	11.21	11.94	12.37

Endurance times in minutes, two decimals. SD boys: 1.64 min; SD girls: 1.20 min

The HR was monitored before and during both exercise tests. In both protocols the children's mean HR at baseline was 99 (SD 13) bpm. At maximal performance the mean HR in both protocols was 193 (SD 9) bpm. Figure 3 shows the HR increase patterns in the two different protocols.

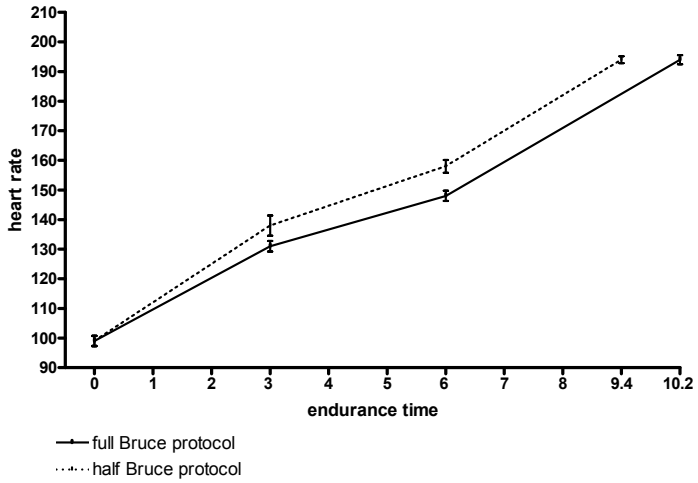

Figure 3 *Increase of heart rate. Continuous line full Bruce protocol; dotted line half-Bruce protocol. Heart rate in bpm, endurance time in min. Paired-samples t-test: difference in heart rate at 3 min, mean difference = 6, SD = 24, p = 0.09; difference in heart rate at 6 min, mean difference = 10, SD = 14, p ≤ 0.01*

Determinants of exercise capacity

Linear regression analysis showed no significant relations between endurance SDS and SDS height (R^2 = 0.002, p = 0.764), SDS BMI (R^2 = 0.001, p = 0.812), SES (R^2 = 0.013, p = 0.722), ethnicity (R^2 = 0.020, p = 0.616), sports participation (R^2 = 0.081, p = 0.127) or school transport habits (R^2 = 0.044, p = 0.336) for the 53 children in group II.

DISCUSSION

The present cross-sectional observational study provides an update of reference values for the original Bruce treadmill protocol in healthy children aged 4 and 5 years. An update was felt necessary as only few and mainly old normative values were available for these young children. Endurance times on the half-Bruce protocol were lower than that on the original Bruce protocol. SDS height, SDS BMI, SES, ethnicity, sports participation and school transport habits were not significantly associated with the SDS endurance time.

We slightly modified the test procedure by permitting the children to hold the guardrails. In our experience, walking on the treadmill with increments of speed and inclination till maximal performance without rail holding is too difficult for many children aged 4 or 5 years. This is why we, in accordance with daily practice, preferred the safety of holding the rail in these young children. Our strategy enabled more young children to perform this maximal exercise test. Rail holding, however, is known to increase endurance time and reduce physiological strain (e.g. HR, VO_2) during sub maximal exercise.[17] And recently, we showed that 6-year-old children, who were not able to perform the Bruce protocol without holding the guardrail, reached longer endurance times than did their age peers.[8] A limitation of our modification is that results cannot easily be compared with those from other studies, because rail holding is not always permitted. Thus, and also in view of other differences in study conditions and the small groups in some studies[5,6] statistical analysis of the differences between studies is not possible. However, deterioration in maximal exercise capacity in Dutch children seems to be likely: for boys the mean endurance time was 9.6 min in the present study and 11.2 min in 1992. For girls the difference was less: 10.1 min in the present study and 10.6 min in 1992.[5] The difference would have been even larger when we had not allowed our children to hold the guardrail. Two studies in North-American children report on exercise testing using the Bruce protocol as well.[6,7] Children in 2002 showed a shorter endurance time on the Bruce treadmill test than those tested in 1977. These findings are consonant with our recent findings that maximal exercise capacity seems to have deteriorated during the past 20 years in children from 6 to 10 years.[8] Longitudinal follow-up studies should be performed to confirm the cross-sectional data of the current study.

In the present study we were not able to identify any determinants of maximal exercise capacity. For children aged 6 - 13 years, however, we earlier found a positive interaction between intensive sports participation and maximal exercise capacity.[8] In children aged 4 and 5 years, the range in sports participation is rather small, which may explain why we did not find a correlation between sports participation and exercise capacity.

One of the secondary aims of the study was to compare the endurance times in the two protocols applied. We found a significant difference of 50 s in endurance time in favor of the original Bruce protocol, which can be explained by the difference in increments in speed and grade between the protocols. In the original protocol, the concurrent speed and grade at the end of each stage is lower than that in the half-Bruce protocol (see Table 1). This probably explains the observed faster increase in HR in the half-Bruce protocol (Figure 3). This phenomenon confirms that there is a difference in strain between the two exercise protocols, resulting in a lower endurance time in the half protocol. On that basis, seeing that these 4- and 5-year-olds could perform the original protocol properly, we think there is no need to use the half-Bruce protocol when using the maximal endurance time as outcome parameter.

A significant learning effect was observed, as reflected by higher endurance times when children performed a second test. Cumming et al.[7] showed high test-retest reproducibility for the Bruce protocol in 20 schoolchildren aged 7 to 13 years. We suggest that 4- and 5-year-olds are more sensitive to the habituation with walking on a treadmill. Therefore, we derived our new reference values only from tests performed by children without former experience with the Bruce treadmill protocol.

In our study we did not measure gas exchange parameters. In a clinical setting there is often no metabolic cart available. Moreover, the use of a facemask or mouthpiece might frighten young children. Cumming et al.[7] reported a strong correlation between the maximal endurance time and maximal oxygen uptake. Endurance time is therefore a good alternative for testing young children in the clinical setting.[7]

CONCLUSIONS

In the current study, we present new reference values for the original Bruce treadmill protocol in healthy children aged 4 and 5 years old. The maximal exercise capacity seems to have deteriorated when we compare our results with those of an earlier study in The Netherlands.[5] The endurance times on the original and the half-Bruce protocol are not interchangeable. So, we recommend to use the original Bruce protocol in these young children and to give them the opportunity to hold the guardrail so that maximal performance can be achieved successfully.

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PART II

CONGENITAL ANOMALIES

Chapter 3
A prospective comparative evaluation of persistent respiratory morbidity in esophageal atresia and congenital diaphragmatic hernia survivors
Saskia J. Gischler, Monique H.M. van der Cammen-van Zijp, Petra Mazer, Gerard C. Madern, Nikolaas M.A. Bax, Johan C. de Jongste, Monique van Dijk, Dick Tibboel, Hanneke IJsselstijn.
Journal of Pediatric Surgery, 2009;44:1683-1690.

Chapter 4
Motor-function and exercise capacity in children with major anatomical congenital anomalies: An evaluation at 5 years of age
Monique H.M. van der Cammen-van Zijp, Saskia J. Gischler, Petra Mazer, Monique van Dijk, Dick Tibboel, Hanneke IJsselstijn.
Early Human Development, 2010 (in press).

Chapter 5
Exercise capacity, fatigue, and level of physical activity in young adults with congenital diaphragmatic hernia
Monique H.M. van der Cammen-van Zijp, Marjolein Spoel, Roxanne Laas, Rita J.G. van den Berg-Emons, Wim C.J. Hop, Johan C. de Jongste, Dick Tibboel, Hanneke IJsselstijn.
Submitted.

Chapter 3

A prospective comparative evaluation of persistent respiratory morbidity in esophageal atresia and congenital diaphragmatic hernia survivors

ABSTRACT

Purpose

The aim of the study was to compare long-term respiratory morbidity in children after repair of esophageal atresia (EA) or congenital diaphragmatic hernia (CDH).

Patients and methods

Children were seen at 6, 12, and 24 months and 5 years within a prospective longitudinal follow-up program in a tertiary children's hospital. Respiratory morbidity and physical condition were evaluated at all moments. At age 5 years, pulmonary function and maximal exercise performance were tested.

Results

In 3 of 23 atresia patients and 10 of 20 hernia patients, bronchopulmonary dysplasia was developed. Seventeen atresia and 11 hernia patients had recurrent respiratory tract infections mainly in the first years of life. At age 5, 25% of EA and CDH patients measured showed reduced forced expiratory volume in 1 second (z-score < −2). Both atresia and hernia patients showed impaired growth, with catch-up growth at 5 years in patients with EA but not in those with hernia. Maximal exercise performance was significantly below normal for both groups.

Conclusions

Esophageal atresia and CDH are associated with equal risk of long-term respiratory morbidity, growth impairment, and disturbed maximal exercise performance. Prospective follow-up of EA patients aimed at identifying respiratory problems other than tracheomalacia should be an integral part of interdisciplinary follow-up programs.

INTRODUCTION

Congenital diaphragmatic hernia (CDH) and esophageal atresia (EA) are both severe congenital anatomical anomalies requiring neonatal surgery and intensive care treatment. Follow-up for children with EA tends to focus on gastrointestinal pathologic condition.[1-3] Respiratory pathologic condition, however, seems equally important and is widely described as related to the variable amount of tracheomalacia. Abnormal development of the tracheobronchial tree may contribute to tracheomalacia and recurrent atelectasis.[4] Mild lung function abnormalities after EA repair have been described.[5,6] Several cross-sectional studies report secondary morbidity. Up to 50% of EA patients were found to have associated anomalies such as cardiac anomalies and consequently higher morbidity.[7] New treatment modalities such as high-frequency oscillation (HFO) ventilation, nitric oxide (NO) administration, and extracorporeal membrane oxygenation (ECMO) have improved survival rates in CDH patients.[8-10] Evidence is emerging, however, that better survival coincides with a great deal of morbidity.[11-17] Long-term pulmonary sequelae in CDH survivors seem to result not only from residual lung hypoplasia with persistent pulmonary hypertension but also from lung injury induced by ventilatory support.[18] Other risk factors for morbidity are large diaphragmatic defects, ECMO therapy, and patch repair.[16]

We hypothesized that children after repair of EA show the same extent of respiratory pathologic condition as CDH survivors, although probably of a different nature, with different causative mechanisms. The aim of the present study was to describe respiratory morbidity in EA and CDH patients with respect to baseline characteristics, respiratory tract infections (RTIs), lung function, and maximal exercise performance. In addition, we evaluated gastrointestinal morbidity and physical growth because these factors may influence the main end points with respect to respiratory morbidity. This is the first study to prospectively evaluate respiratory morbidity in EA patients at the age of 5 years.

METHODS

This longitudinal, observational, prospective, cohort study consists of repeated measurements at 6, 12, and 24 months and at 5 years.

Setting

The facility used for the study was the Pediatric Surgical Department of the Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands. This is the only tertiary academic facility in the Southwestern part of the Netherlands equipped for all major surgical specialties. The referral area has 4 million inhabitants with 44,000 newborns annually.

Since 1999, a multidisciplinary team -consisting of a consultant senior pediatric surgeon, pediatricians, psychologists, a pediatric physiotherapist, nurses, and a social worker- runs a follow-up program for children born with a major anatomical malformation and their families. A clinical geneticist was added to the team in 2004. The program aims to reduce the overall morbidity associated with these malformations, in particular, the index diagnoses as described by Ravitch.[19]

Patients

All 68 patients with EA and CDH admitted to the ICU of our department within 7 days after birth from January 1999 to February 2003 were eligible for this study. For the present study, we excluded data from 4 patients having infections and growth impairment as a result of a major syndromal or chromosomal anomaly itself (EA, n = 3, 2 Down's syndrome and 1 undefined; CDH, n = 1, Wolf-Hirschhorn syndrome). Data of the 16 children who died within 6 months were excluded as well. Five families did not participate in our follow-up program. Thus, 43 children (82.7% of survivors) completed a 5-year follow-up (Figure 1).

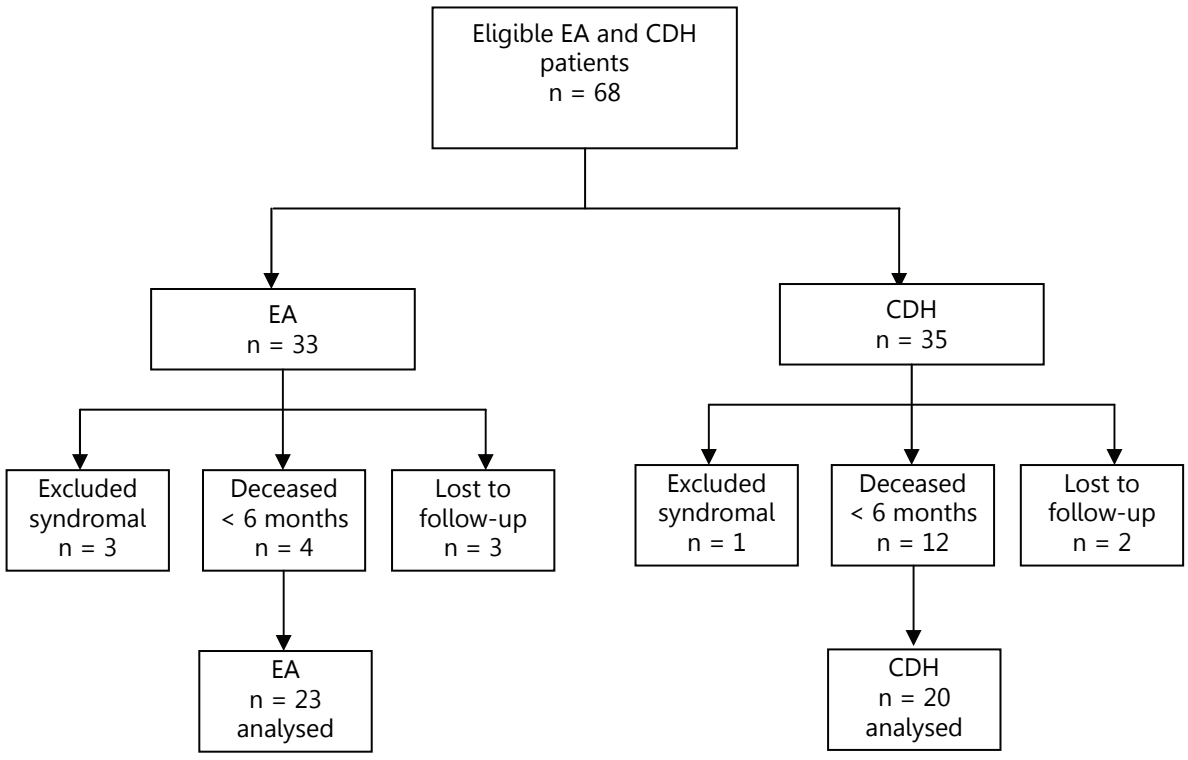

Figure 1 *Flowchart showing group composition*

Procedure

The Erasmus MC ethical review board agreed with the study, and written parental informed consent was obtained for all subjects. Demographic and medical data were collected prospectively from the first day of admission. A clinical geneticist routinely evaluated major chromosomal, syndromal and cerebral abnormalities during admission. By protocol, the children were seen at ages 6, 12, and 24 months and 5 years, corrected for gestational age. Age for the final evaluation ranged from 5 to 6.5 years.

General aspects

At each time-point, a pediatrician performed a full physical examination including neurologic examination according to the method of Touwen.[20] A senior pediatric surgeon evaluated specific pediatric surgical issues. Weight and height were measured, and body mass index (BMI) was calculated. Growth data for the Dutch population served as reference values[21,22] and standard deviation scores (SDS) were calculated using Growth Analyser version 3.5 (Dutch Growth Foundation, Rotterdam, The Netherlands). Reference values for Dutch children of Moroccan or Turkish origin were used if applicable.[23,24]

Respiratory morbidity

The incidence and severity of bronchopulmonary dysplasia (BPD) were recorded according to the diagnostic criteria of Jobe and Bancalari.[25]

At each time-point, therapeutic and prophylactic courses of antibiotic treatment, use of inhaled bronchodilators and steroids, and readmissions for RTI were recorded. We recorded numbers of RTI during the first, the second, and the third to fifth years, respectively. At the age of 5 years, 38 children (EA patients, n = 20, and CDH patients, n = 18) performed pulmonary function tests as follows: we obtained flow-volume curves before and after bronchodilation with 400 µg of salbutamol and measured the fraction of exhaled NO (FE_{NO}). Flow-volume curves were measured on a Masterscreen electronic spirometer (Jaeger, Würzburg, Germany). Forced expiratory volume in 1 second (FEV_1) was expressed as percentage predicted. Fraction of exhaled NO was measured online according to guidelines from the European Respiratory Society and American Thoracic Society using the NIOX analyzer (Aerocrine, Solna, Sweden).[26]

Maximal exercise performance

At 5 years, the children performed a graded, maximum exercise test using a motor-driven treadmill (En Mill, Enraf Nonius, Rotterdam, the Netherlands) programmed for increases in angle of inclination and speed according to the Bruce protocol.[27]

The children were encouraged to perform to voluntary 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 (personal communication, van der Cammen-van Zijp, May 2008). Before, during, and at 2 and 5 minutes after the test, children's heart rate and transcutaneous oxygen saturation were monitored with a pulse oximeter (MARS [motion artifact system], type 2001, Respironics Novametrix, Murrysville, Pa). Heart rate of at least 185 beats per minute or loss of coordination was considered to indicate maximal performance.[28]

Gastrointestinal morbidity

Children were evaluated for gastroesophageal reflux (GER) by barium swallow x-ray and pH-metry as previously described by Bergmeijer.[29,30] Gastrointestinal symptoms, use of medication, surgical treatment of reflux, and consultation of a dietician were recorded as well.

Data analyses

Descriptive statistics were calculated for baseline characteristics and outcome variables. We performed group comparisons with the Mann-Whitney U test. Growth parameters and SDS maximal endurance time were compared with the reference values using t-tests for independent samples (1-tailed). Statistical significance was accepted at 5% level. SPSS 15.0 for Windows (SPSS, Chicago, Ill) was used for data analyses.

RESULTS

Baseline characteristics for both groups of children are shown in Table 1. All CDH patients were born after a gestational age of at least 36 weeks; 4 EA patients were born before 36 weeks of gestation at 28, 29, 31, and 33 weeks, respectively. All but one EA children underwent primary anastomosis via a lateral thoracotomy within 48 hours. One patient had a type A long gap atresia and underwent delayed primary anastomosis after 3 months. Bronchoscopic evaluation of tracheomalacia during the initial repair was not routinely performed. In 15 of the 20 children with CDH (75%), the diaphragmatic defect was repaired with a Gore-Tex patch (WL Gore and Associates, Flagstaff, Ariz). Only one child had a right-sided CDH (5%). Diaphragmatic repair was by subcostal laparotomy in all cases.

In neither group complex heart defects were found. For both groups, the major impact of morbidity was during the first year of life; hospital admissions occurred mainly in the first 6 months and surgical interventions within the first year. Surgical interventions in EA patients comprised mainly dilations of anastomotic esophageal strictures (in 70% of EA patients, n = 16, median 2 per patient, range 0 - 9) and Nissen fundoplications (n = 8, 34.8%). Aortopexies had not been performed.

Table 1 *Baseline characteristics distinguished by CA subgroup*

	EA	**CDH**
	n = 23	n = 20
Boys, n (%)	15 (65.2)	12 (54.5)
Gestational age, mean (SD), wk	37.2 (3.5)	39.2 (1.5)
Birth weight, mean (SD), kg	2.7 (0.8)	3.4 (0.3)
Patients without additional (major or minor) CA, n (%)	5 (21.7)	12 (60.0)
Patients with 1 or more additional major CA, n (%)	6 (26.1)	3 (15.0)
Patients with 1 or more additional minor CA, n (%)	14 (60.9)	5 (25.0)
Patients with cardiac anomaly, n (%) (ASD, VSD, Coarctation of aorta)	4 (17.4)	2 (10.0)
Admission in 1st 24 mo, median (range), d	60.0 (11 - 181)	67.5 (15 - 192)
Surgical interventions in 24 mo, median (range), n	5 (1 - 11)	3 (1 - 6)
Ventilatory support, median (range), d	3.5 (1 - 44)	19.5 (2 - 62)
Supplemental oxygen, median (range), d	6.0 (1 - 77)	37.5 (3 - 83)
Patients with additional medical problems at discharge, n (%)	20 (86.9)	18 (90.0)
Patients with additional medical problems at 5 y, n (%)	21 (91.3)	18 (90.0)
Additional medical problems per patient at discharge, median (range)	2 (0 - 12)	2 (0 - 6)
Additional medical problems per patient at 5 y, median (range)	2 (0 - 7)	2 (0 - 10)

CA: congenital anomaly, ASD: atrial septal defect, VSD: ventricular septal defect

Additional medical problems at discharge varied from GER (n = 21 EA; n = 18 CDH) to atopic eczema and were mainly (> 80% for each group) related to the primary congenital anomaly. At discharge, 21 (87%) of EA patients and all CDH patients received medication. These figures had dropped to 43.5% and 23.8% at the age of 5 years, respectively.

Respiratory morbidity

All EA patients had been ventilated conventionally. Three children (13%) with severe tracheomalacia developed BPD (Table 2), and bronchoscopy was performed only in these 3 patients. None of the EA patients received ECMO treatment.

Eight CDH patients (40%) were primarily ventilated with HFO and had been converted to conventional ventilation before surgical closure of the diaphragm. Four (33.3%) of the conventionally ventilated CDH patients were later converted to HFO ventilation. Venoarterial ECMO was performed in 11 CDH patients (55%), starting at a median age of 13 (range 5 - 265) hours. Extracorporeal membrane oxygenation was discontinued after a median of 168 (72 - 459) hours.

Routine vaccination against respiratory syncytial virus and/or influenza was not performed.

Table 2 *Respiratory morbidity in EA and CDH patients during the first 5 years of life*

		EA	**CDH**
		n = 23	n = 20
Patients with BPD, n (%)	none	19 (82.7)	8 (40.0)
	mild	1 (4.3)	2 (10.0)
	moderate	1 (4.3)	2 (10.0)
	severe	2 (8.7)	8 (40.0)
Total number of RTI in 5 yrs, median (range)		9 (0 - 27)	7 (0 - 17)
Patients with > 5 RTI in 5 years, n (%)		17 (73.9)	11 (55.0)
Number of patients admitted for RTI in 5 years, median (range)		0 (0 - 4)	0 (0 - 1)
Number of therapeutic courses of antibiotics for RTI, median (range)		3.0 (0 - 17)	3.0 (0 - 8)
	1st year	1.0 (0 - 6)	1.0 (0 - 4)
	2nd year	1.0 (0 - 4)	1.0 (0 - 3)
	3 - 5 years	0.0 (0 - 10)	0.0 (0 - 3)
Patients treated with prophylactic antibiotics for RTI, n (%)			
	1st year	3 (13.0)	0
	2nd year	5 (21.7)	3 (15.0)
	3 - 5 years	6 (26.1)	0
Use of bronchodilators, n (%)		6 (26.1)	5 (25.0)
Use of inhaled steroids, n (%)		2 (8.7)	2 (10.0)
FEV_1 before bronchodilation, mean % predicted (range)		85 (69 - 118) n = 12	91 (72 - 122) n = 8
Patients with abnormal FEV_1 (Z-score < -2), n (%)		3 (25.0)	2 (25.0)
FE_{NO}, median parts-per-billion (range)		9.0 (5.0 - 20.4)	5.2 (2.8 - 10.0)

Table 2 gives details of the respiratory morbidity encountered during the 5 years of follow-up. Both EA patients born before 30 weeks of gestation developed BPD; only one of them had recurrent RTI. Nine (81.1%) of 11 ECMO-treated CDH patients and one other developed moderate or severe BPD. Of these 10, 5 (50%) had recurrent RTI. Recurrent RTI were also reported in 6 CDH patients (60%) who had absence of or only mild BPD. One prematurely born EA patient and both CDH patients with a cardiac anomaly developed BPD. None of them had recurrent RTI.
Hospitalizations for RTI were rare. Median numbers of RTI are relatively low but show wide ranges in both groups.

Spirometry before and after bronchodilation was initiated in 38 patients at 5 years; 5 patients were not examined because of parental refusal (n = 2), for practical reasons (n = 2), or because of mental retardation (n = 1). Most patients, however, failed to perform reproducible flow-volume curves. Forced expiratory volume in 1 second and FE_{NO} were the only 2 reliably obtained lung function parameters (Table 2). In both groups, 25% (n = 12 EA, 8 CDH) of patients had abnormally low percentage of predicted of FEV_1. The median FE_{NO} was within the predicted range for (n = 9) EA patients (9.0 parts-per-billion) and in the lower range of normal for (n = 9) CDH patients (5.2 parts-per-billion).[31]

Maximal exercise performance

One EA patient and 2 CDH patients could not perform the maximal exercise test because of neurologic underlying disease such as cerebral palsy. Thus, 22 EA patients and 18 CDH patients performed the exercise test. Reliable results could not be obtained for 6 EA patients for the following reasons: no maximal exercise performance reached (n = 3); balance problems (n = 2); and poor concentration (n = 1). Results for 2 of the CDH patients were unreliable because of balance problems or unwillingness to perform maximally (n = 1 for each reason).

Both in EA (n = 16) and CDH (n = 16) patients, the maximal exercise tolerance was significantly below the norm (mean SDS endurance time, -0.60; p = 0.02, and -0.84; p = 0.012, respectively). One EA patient (6.3%) and 2 CDH patients (12.5%) had an abnormally low maximal exercise tolerance (ie, maximal endurance time SDS < −2; not significant). The median (range) heart rate at maximal exercise was 181 (194 - 148) and 191 (207 - 146) beats per minute for the EA and CDH group, respectively. Two EA patients (12.5%) had a decreased oxygen saturation (ie, ≤ 94%) at maximal exercise (94 and 93%, respectively). This phenomenon was not observed in any of the CDH patients.

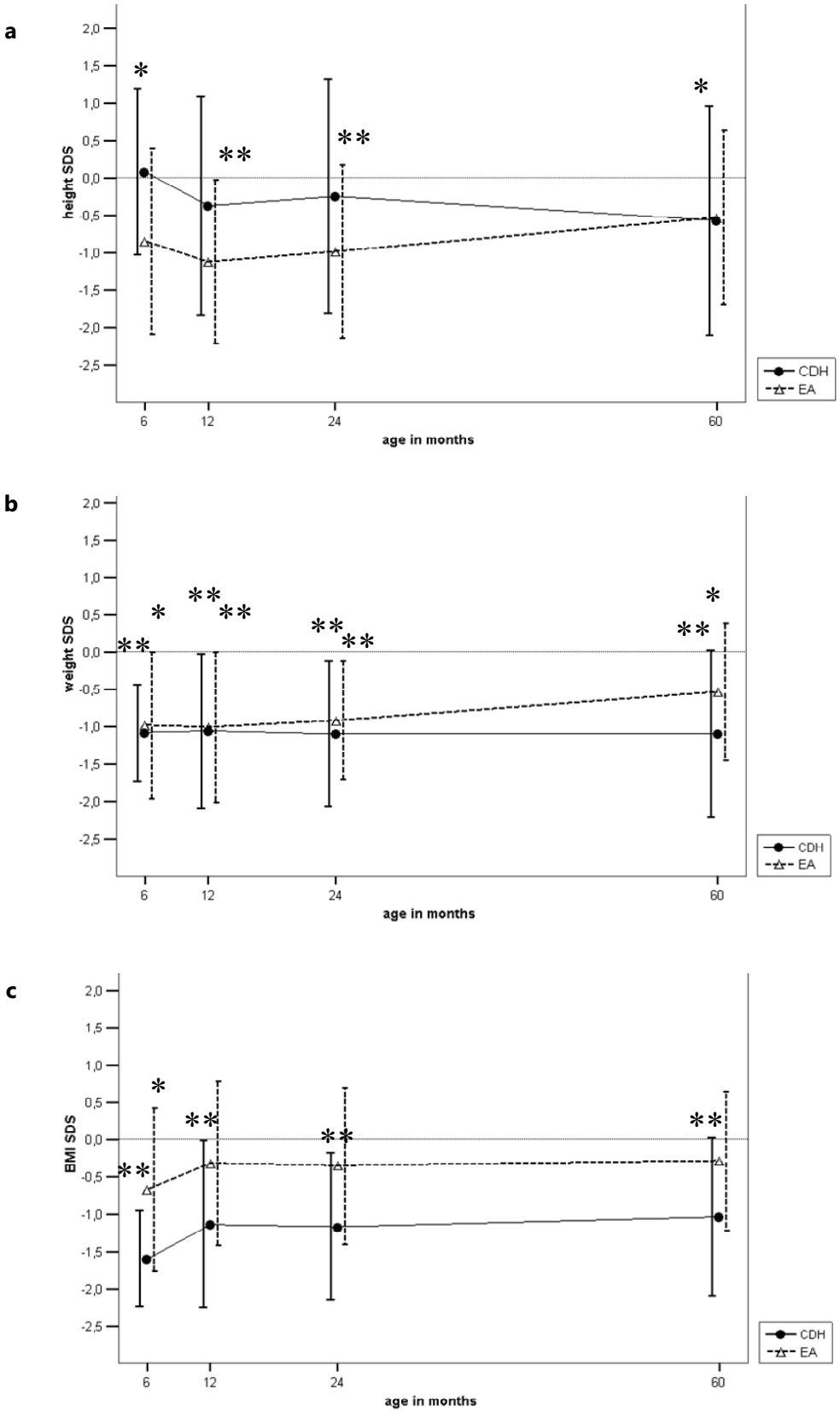

Figure 2(a, b, and c) *Diagram representing the mean (SD) for height (a), weight (b), and BMI (c) across time in CDH and EA patients. Circles and solid lines represent CDH; open triangles and dashed lines represent EA. * signals significant deviation from the Dutch norm at the 5% level (p ≤ 0.05), ** signals significant deviation from this norm at the 0.1% level (p ≤ 0.001)*

Gastrointestinal morbidity

In both groups, 20 children were treated conservatively with antacids and prokinetic drugs initially. Thirteen EA patients and 11 CDH patients also received an acid secretion inhibitor. Eight EA patients (34.8%) and 7 CDH patients (35%), respectively, underwent a Nissen fundoplication. For those patients who were treated conservatively, the median (range) duration of treatment of GER was 23.11 (0 - 71.7) and 8.0 (0 - 64.9) months in EA and CDH, respectively. Patients with EA who underwent a Nissen fundoplication had a median number of 9.5 RTI in 5 years (range, 0 - 23) vs 7 (3 - 24) for those treated conservatively (NS). Corresponding figures for the CDH patients are 9 (1 - 17) vs 7 (0 - 14) (NS). There was no significant difference in RTI before or after the Nissen fundoplication.

A dietician was consulted for 8 patients in each group.

Physical growth

Data at 6, 12, 24, and 60 months for both groups are shown in Figure 2. At 5 years of age, EA patients seemed to catch up in weight, concomitant with an increase in height (Figure 2b and a). The BMI SDS was constant after the first year of life for both groups but reached a higher level for EA patients (Figure 2c).

Extracorporeal membrane oxygenation-treated CDH patients had a significantly lower height at 6 months, 12 months, and 5 years ($p = 0.02$, 0.04, and 0.04, respectively), lower weight at 12 months and 5 years ($p = 0.02$ and 0.02, respectively), and lower BMI at 12 months of age ($p = 0.05$) than non-ECMO-treated CDH patients.

Discussion

We prospectively evaluated respiratory morbidity and factors interrelating with pulmonary disease during the first 5 years in 2 groups of children born with major congenital anatomical malformations of the respiratory tract: EA and CDH. Both groups showed recurrent respiratory tract infections, abnormally low FEV_1 in 25% of patients, no increase of FE_{NO} levels, and decreased maximal exercise tolerance. In addition, a high incidence of GER and impaired physical growth were observed in both groups.

Tracheomalacia associated with EA occurs frequently and may lead to respiratory insults.[32] Less frequent are RTIs, wheezing, and cough; these findings mainly are derived from studies using a cross-sectional design.[33-36] Results, especially regarding RTIs, therefore may have been influenced by recall bias. Dudley and Phelan[37] retrospectively evaluated 192 EA survivors and found that 78 children had experienced more than 3 episodes of bronchitis per year in the first 3 years of life. More recent, Malmström et al[34]

showed that 41% of adolescents after repair of EA still had respiratory symptoms, and 52% had ever had pneumonia or wheezing. Pneumonia in the first years of life may give rise to mild lung function abnormalities later in life.[38] Our prospectively collected data are consistent with these findings. In addition, we showed that these problems might negatively affect maximal exercise tolerance. Only 3 EA patients with severe tracheomalacia required prolonged ventilation and developed BPD, whereas 10 (50%) CDH patients, mainly those treated with ECMO, had moderate to severe BPD according to criteria of Jobe and Bancalari.[25] We assume, therefore, that different mechanisms are involved in persisting respiratory morbidity. In CDH patients, the susceptibility of the hypoplastic lungs for artificial ventilatory support is well documented.[13,39,40]

In both groups, the frequency of RTI at any measurement moment did not differ between children who underwent a Nissen fundoplication for GER or those who were treated conservatively. We assume that reflux in these patients is not a major contributor to RTI.

Interestingly, hospital admissions for RTI were hardly needed, and therapeutic antibiotic courses had not always been prescribed. This suggests that many RTIs showed a relatively mild course and were of nonbacterial origin.

As sample sizes were limited and numbers of possible contributing factors large, we did not perform regression analysis to predict respiratory morbidity. Still, we evaluated several factors that might have contributed to RTI. Being rare in either group, cardiac anomalies did not seem to influence incidences of RTI within the first 5 years. Because 50% to 60% of CDH patients showed recurrent RTI irrespective of BPD, we assume that extrapulmonary factors may be involved as well. Most patients in either group had gastrointestinal problems and impaired physical growth. These factors may well contribute to increased susceptibility for RTI. Nevertheless, the impact of gastrointestinal problems on RTI in EA patients remains inconclusive so far.[34,37,38]

Pulmonary function testing proved problematic. For no more than half of the patients (n = 20), we could interpret FEV_1 before bronchodilation. This revealed airflow obstruction in 25% of them. From the literature, it appears that pulmonary function testing was successful in 40% to 83% of 5-year-old children.[41]

Fraction of exhaled NO is known to be associated with eosinophilic airway inflammation.[31,42] Almost all patients in the present study had normal FE_{NO} levels, in line with findings by Malmström et al.[34] The FE_{NO} level was increased in only one CDH patient, who showed an atopic constitution. Low or normal FE_{NO} levels have also been described in children with bronchopulmonary dysplasia,[25] which might explain the lower median FE_{NO} in the CDH patients.

Both EA and CDH patients showed lower maximal exercise tolerance compared with recently established reference values for healthy Dutch children (personal communication, Van der Cammen-van Zijp). Persistent respiratory morbidity and impaired growth may contribute to this phenomenon.

In spite of gastrointestinal and nutritional morbidity, especially in the first year for EA patients, only 13% of parents consulted with a dietician during the child's first year of life. For the CDH patients, failure to thrive remained a problem over time. Lack of catch-up growth was mainly seen in ECMO-treated CDH patients. We assume that they have more severe lung hypoplasia requiring intensive work of breathing. Patch repair, GER, and recurrent RTI may also contribute, but our data do not allow for hard conclusions. Attempts should be undertaken to improve energy intake as work of breathing may require a higher energy intake in CDH and, to a lesser extent, EA patients.

Multidisciplinary follow-up of surgical newborns has hardly been performed so far but has recently been advocated by the American Academy of Pediatrics for CDH patients.[43] The groups of Muratore and Friedman,[15-17] however, have reported retrospectively collected data on pulmonary, gastrointestinal, and neurodevelopmental morbidity in CDH patients up to 3 years of age in a multidisciplinary follow-up clinic. It appeared that these showed continued pulmonary and gastrointestinal morbidity over the years, such as the CDH patients in the present study, who show the same pathologic condition up to the age of 5 years.

In conclusion, both EA and CDH patients are at risk for long-term respiratory morbidity, disturbed maximal exercise performance, and growth impairment. Prospective evaluation of EA patients aimed at identifying other respiratory problems than tracheomalacia should be an integral part of postoperative interdisciplinary follow-up programs.

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Chapter 4

Motor-function and exercise capacity in children with major anatomical congenital anomalies:
An evaluation at 5 years of age

ABSTRACT

Background

Children with major anatomical congenital anomalies (CA) often need prolonged hospitalization with surgical interventions in the neonatal period and thereafter. Better intensive care treatment has reduced mortality rates, but at the cost of more morbidity.

Aim

To study motor-function and exercise capacity in five-year-old children born with CA, and to determine whether motor-function and exercise capacity differ according to primary diagnosis.

Study design

Descriptive study.

Subjects

One hundred and two children with the following CA: congenital diaphragmatic hernia (CDH) n = 24, esophageal atresia (EA) n = 29, small intestinal anomalies (SIA) n = 25, and abdominal wall defects (AWD) n = 24.

Outcome measures

Overall and subtest percentile scores of the Movement Assessment Battery for Children (MABC) were used to measure motor skills. Endurance time on the Bruce treadmill test was used to determine maximal exercise capacity.

Results

Motor-function: Seventy-three children (71.6%) had an overall percentile score within the normal range, 18 (17.6%) were classified as borderline, and 11 (10.8%) had a motor problem. This distribution was different from that in the reference population (Chi-square: p = 0.001). Most problems were encountered in children with CDH and EA (p = 0.001 and 0.013, respectively). Ball skills and balance were most affected.

Exercise capacity: Mean standard deviation score (SDS) endurance time = -0.5 (SD: 1.3); p = 0.001; due to poor exercise performance in CDH and EA patients.

Conclusions

Children with major anatomical CA and especially those with CDH and EA are at risk for delayed motor-function and disturbed exercise capacity.

INTRODUCTION

Annually some 5,500 newborns (about 3% of all births) in the Netherlands present with major anatomical congenital anomalies (CA).[1] Children with major anatomical CA often need prolonged hospitalization with (multiple) surgical interventions in the neonatal period and thereafter. Better intensive care treatment has reduced mortality rates, but at the cost of more morbidity. It is therefore that the department of Pediatric Surgery of our tertiary hospital started in 1999 a multidisciplinary follow-up program for children born with CA and their families.[2] The aim of the program is to evaluate and to reduce the overall morbidity associated with the malformations of the children. Within this follow-up program, children with CA are tested at fixed time points. We have recently shown that children with major CA suffer from psychomotor developmental delay within the first two years of life.[2] And, a recent evaluation of persistent respiratory morbidity in children born with esophageal atresia (EA) and congenital diaphragmatic hernia (CDH) revealed disturbed exercise capacity in 5-year-old-survivors.[3] Further standardized assessment of motor-function and exercise capacity in school-aged children with major CA other than cardiac malformations has hardly been published.[4,5] Early identification of children with motor impairments however, is important to provide support and intervention for the child as early as necessary, since motor problems do not disappear spontaneously.[6]

The aim of the present study was to determine whether 5-year-old children with different major CA are at risk for impaired motor-function and reduced exercise capacity, and to determine whether motor-function and exercise capacity differ according to primary diagnosis. We evaluated four different groups of CA patients: children born with CDH, EA, small intestinal anomalies (SIA), and abdominal wall defects (AWD).

METHODS

Participants

Between January 1999 and December 2003, 204 newborns with CDH, EA, SIA or AWD were admitted to our pediatric surgical intensive care unit within seven days of birth. As twenty-six of these babies died (CDH n = 14; EA n = 5; SIA n = 5; AWD n = 2), 178 were eligible for follow-up. The parents of 35 children declined to participate. By the age of five years, 15 children had not been assessed for logistic reasons. Twenty-six children were not testable and thus excluded from analysis: 19 with syndromal or chromosomal disorders (CDH n = 3; EA n = 4; SIA n = 10; AWD n = 2), six with neurological impairments (CDH n = 2; EA n = 1; SIA n = 1; AWD n = 2), and one child (with AWD) with behavior problems. Finally, 102 of 178 eligible children (57.3%) participated in this study (Figure 1). The Medical Ethical Review Board approved the follow-up program, and written parental informed consent was obtained.

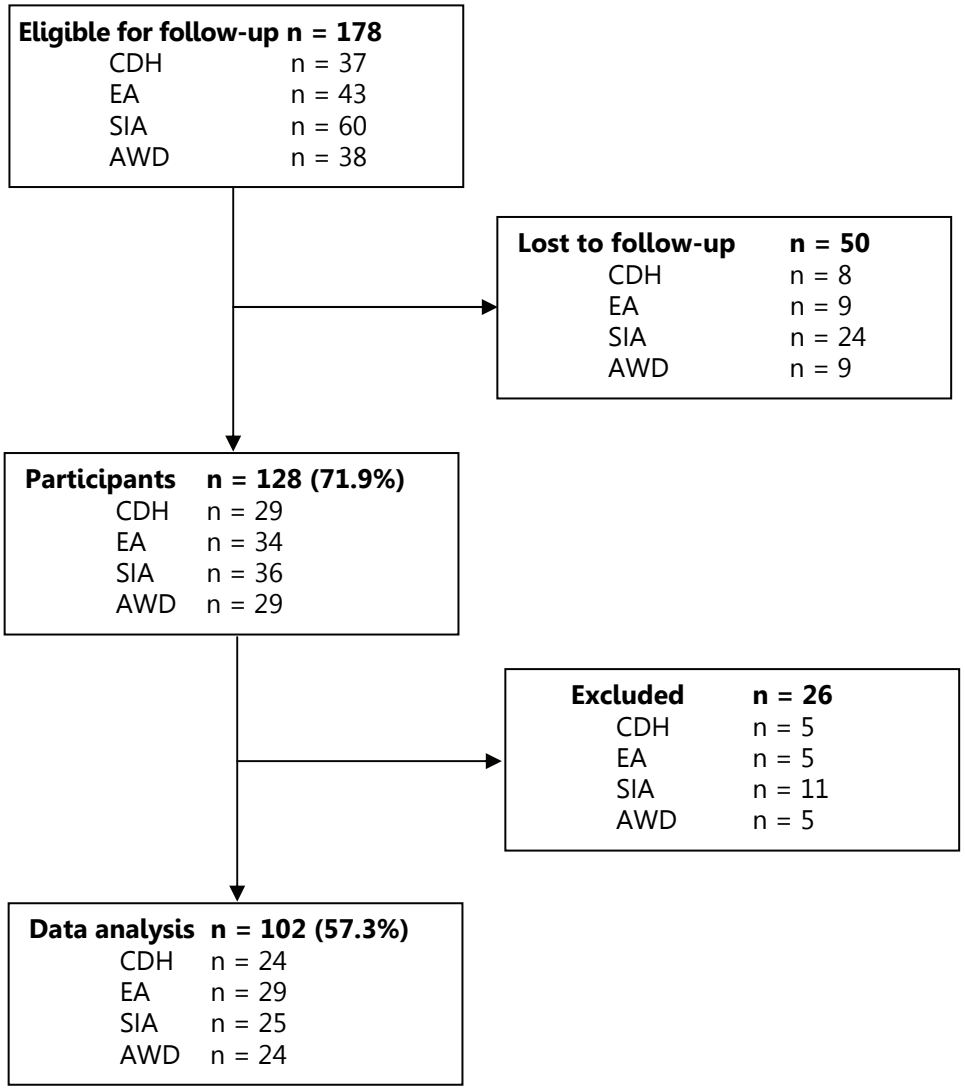

Figure 1 *flow chart*

Procedure

General

Since 1999, the multidisciplinary team has prospectively performed follow-up for neonates with major CA treated in the pediatric surgical department at our tertiary children's hospital. The following data were collected prospectively: gestational age, birth weight, major CA, duration of artificial ventilation, number and duration of hospital admissions, and number of surgical interventions. Small for gestational age (SGA) was defined as birth weight < -2SD for gestational age. These baseline data were also retrieved for 50 children who were lost to follow-up. Major chromosomal, syndromal and cerebral abnormalities were routinely evaluated. From the medical records we retrieved data on results of cerebral ultrasound examinations and MR-imaging of the brain.

By protocol the children were seen at ages 6, 12 and 24 months, corrected for gestational age, and at 5 years.[2] The evaluation at age 5 years refers to evaluation between 5 and 6.5 years of age (mean age 5.7 years). A pediatrician performed a physical examination, including neurological examination and measurement of height and weight. Previously published data on growth for the Dutch population[7,8] served as reference values, and we calculated standard deviation scores (SDS) for height, weight, and body mass index (BMI) using Growth Analyzer version 3.5 (Dutch Growth Foundation). The existence of visual impairment, physical abnormalities interfering with motor-function, and treatment by physiotherapist was recorded.

Motor-function assessment

The MABC was used to evaluate the children's motor skills. The test evaluates motor-function in daily life and is suitable for children without neurological impairments who can understand and act on instructions. A Dutch standardization study has shown that the original norm scores and cut off points can also be applied to Dutch children.[9] Good validity and reliability have been demonstrated.[10] Because all children were younger than 7 years tasks from age band I (4 - 6 years) were used. The MABC consists of eight items: three manual dexterity items; two ball-skill items; and three balance items. Scores for each item were provided; these ranged from good (0) to very poor (5). A profile of the child's motor performance for each domain of the test was obtained by summing the relevant item scores. Summation of all item scores produces the total impairment score (TIS). The three subtest scores and the TIS can be interpreted using age-related normative data tables. The range between the 100th and 16th percentile is regarded as "normal"; between the 15th to 6th percentile as "borderline". The 5th percentile and below is regarded as a "definite motor problem".[9,11] All tests were administered by an experienced pediatric physiotherapist.

Exercise capacity

The children performed a graded, maximum exercise test using a motor-driven treadmill (En Mill, Enraf Nonius, Rotterdam, the Netherlands) programmed for increases in angle of inclination and speed according to the Bruce protocol.[12,13] The children were encouraged to perform to voluntary exhaustion. The maximal endurance time (in minutes, one decimal) served as criterion of exercise capacity. Before and during the test heart rate and transcutaneous oxygen saturation were monitored with a pulse Oximeter (motion artifact system, type 2001, Respironics Novametrics, Murrysville, PA, USA). Maximal performance was indicated by a HR of ≥ 185 beats per minute (bpm) or loss of coordination.[14] The SDS of the maximal endurance time was calculated using recently age-related established reference values for healthy Dutch children.[12,13]

Statistical analysis

Unless stated otherwise, data are presented as mean (SD). One-sample t-tests were used to test whether the SDS of growth parameters and the maximal endurance time were different from those of the norm population. Non-parametric tests were used to perform group comparisons. A Chi-square test was applied to test whether the distribution of motor performance scores in our population differed significantly from that in the normative population. Spearman Rank correlation coefficients (r_s) were calculated to evaluate the association between motor performance scores on the one hand and baseline variables, and growth data on the other hand. The Kruskal Wallis test was used to measure group differences. Statistical significance was accepted at a 5% level. Analyses were performed using SPSS 15.0.

RESULTS

Cerebral ultrasound examinations performed within the first weeks of life were abnormal in 4 patients: hyperdense lesions reflecting perinatal asphyxia were seen in 2 CDH and 1 SIA patient and 1 EA patient had benign hydrocephalus. In addition, another EA patient had signs of delayed myelinisation on MRI at 4 months. Baseline characteristics for participants are shown in Table 1. From the 10 children with cardiac malformation 4 needed cardiac surgical intervention (coarctation of the aorta n = 3 (2 of them with additional septal defects); atrial septal defect n = 1). The other 6 patients with septal defects (n = 4) and mild coarctation of the aorta (n = 2) were not operated on.

Participating CDH patients were hospitalized longer in the first 6 months after birth and had more hospital admissions between 6 and 24 months ($p = 0.002$ and $p = 0.037$ respectively) than children who were lost to follow-up. Participating children had more often Dutch parents than the children in the missing group ($p < 0.001$). All other baseline characteristics in participants and missing patients were not significantly different (data not shown).

The characteristics at age 5 are presented in Table 2. Two patients suffered from seizures after the neonatal period; subsequent MR-imaging of the brain was normal. Prior to the evaluation of motor skills, a pediatrician performed a physical examination, including neurological examination. Six children were found to have minor neurological dysfunction, varying from mild mental retardation (n = 3), amyotrophic shoulder neuralgia (n = 1), and mild hypotony (n = 1).

Table 1 *Baseline characteristics*

	CDH	**EA**	**SIA**	**AWD**
	n = 24	n = 29	n = 25	n = 24
Boys, n (%)	13 (54.2)	16 (66.7)	13 (52.0)	10(41.7)
Gestational age, wk	39.4 (36 - 41.4)	38.4 (28.6 - 42.0)	36.9 (29.6 - 41.7)	38 (33.6 - 41.9)
Birth weight, kg	3.2 (1.8 - 4.0)	2.9 (0.8 - 4.5)	2.8 (1.6 - 3.6)	2.5 (2.1 - 4.4)
SGA, n (%)	0 (0)	4 (13.8)	0 (0)	4 (16.7)
Patients with ≥ 1 additional major CA, n (%)	5 (20.8)	9 (31.0)	4 (16.0)	6 (25.0)
Dutch parents, n (%)	21 (87.5)	26 (89.7)	23 (92.0)	22 (91.7)
Cardiac malformation, n (%)	1 (4.2)	4 (13.8)	4 (16.0)	1 (4.2)
Ventilatory support, days*	21 (2 - 62)	3 (1 - 44)	2 (0 - 18)	2 (0 - 192)
Hospital admission first 6 months, days	53.5 (14 - 167)	50 (11 - 168)	29 (6 - 184)	33 (7 - 182)
Hospital admission between 6 and 24 months, days	1 (0 - 31)	3 (0 - 93)	0 (0 - 23)	0 (0 - 29)
Hospital admission 24 months to 5 years*, days	0 (0 - 18)	0 (0 - 31)	0 (0)	0 (0 - 47)
Surgical interventions in 24 months*	3 (1 - 7)	6 (1 - 18)	2 (1 - 5)	1.5 (1 - 6)
ECMO, n (%)*	11 (45.8)	0 (0)	0 (0)	0 (0)

Presented are the baseline characteristics of the group of 102 children available for analysis
SGA = small for gestational age; ECMO = extracorporeal membrane oxygenation; Data are presented as number (%) of patients or median (range);
** $p < 0.01$ Kruskal Wallis (differences between groups)*

Table 2 *Characteristics of the study group at 5 years of age*

	CDH	EA	SIA	AWD
	n = 24	n = 29	n = 25	n = 24
Age in years	5.7 (0.4)	5.9 (0.5)	5.9 (0.4)	5.6 (0.3)
Weight SD score[#]	-1.3 (1.0)*	-0.5 (0.9)*	-0.6 (1.0)*	-1.0 (1.3)*
Height SD score	-0.8 (1.4)[§]	-0.6 (1.1)*	-0.3 (1.1)	-0.8 (1.2)*
BMI SD score[†]	-1.2 (0.8)*	-0.2 (0.9)	-0.4 (0.9)[§]	-0.6 (1.0)*
Physiotherapy at age 5, n (%)	3 (12.5)	7 (24.1)	4 (16.0)	0 (0)

Data are presented as number (%) of patients or mean (SD)
[#] *p < 0.05 Kruskal Wallis (differences between groups)*
* *p < 0.01 one sample t-test (SDS significant below zero)*
[§] *p < 0.05 one sample t-test (SDS significant below zero)*
[†] *p < 0.01 Kruskal Wallis (differences between groups)*

All 102 children were tested using the MABC (Table 3 and Figure 2). Seventy-three children (71.6% vs 85.0% expected) had a TIS within the normal range, eighteen children (17.6% vs 10.0% expected) were classified as borderline, and another eleven (10.8% vs 5.0% expected) as having a motor problem. This distribution is significantly different from reference values (Chi square p = 0.001). The six children with neurological impairments due to cerebral palsy were excluded and not tested. When added to the eleven children with a percentile score representing a definite motor problem, 17 of 108 (15.7%) had a definite motor problem.

Most problems were encountered with ball skills (Chi square p < 0.001) and balance (Chi square p < 0.001) but not with manual dexterity. TIS of the children with CDH and EA differed significantly from the reference population (p = 0.001 and 0.013, respectively). Ball skills were impaired in CDH and EA patients; children with EA also had problems with balance (Figure 2).

Maximal exercise performance data were analyzed for 82 (80.4%) children because 20 children did not reach maximal performance according to our pre-defined criteria (CDH n = 2, EA n = 7, SIA n = 6, AWD n = 5). Overall, these 82 children performed worse than the reference population: mean SDS endurance time = -0.49; p = 0.001, due to poor maximal exercise performance in CDH and EA patients (Table 3).

The percentile score on the MABC correlated negatively with the total number of major CA (r_s = -0.27, p = 0.007), and positively with the SDS of the maximal endurance time (r_s = 0.33; p = 0.002). A significant negative correlation was also found with duration of hospitalization and number of surgical interventions (r_s = -0.29; p = 0.003 and r_s = -0.27; p = 0.006). No significant correlation was found between the MABC score and growth parameters.

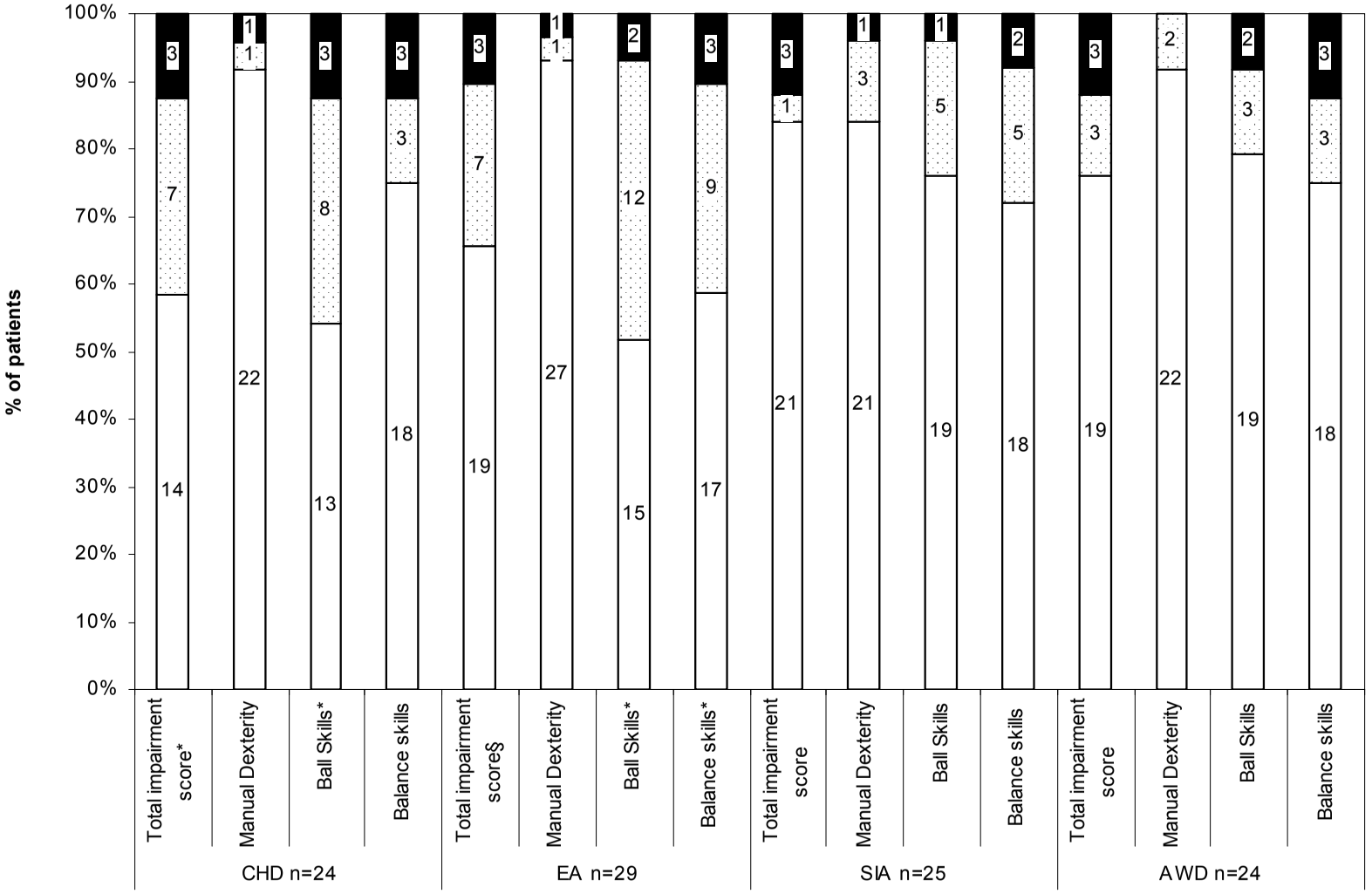

Figure 2 *MABC scores for different groups; For each group TIS and sub-scores are shown.*
Normal range (> P 15, open bar); Borderline range (P 6 - P 15, stippled bar); Definitive motor problem (≤ P 5, black bar)
** p < 0.01 chi square (difference from norm values)*
§ p < 0.05 chi square (difference from norm values)

Table 3 *Overall results of motor-function performance and maximal exercise capacity*

	CDH	EA	SIA	AWD	Total
	n = 24	n = 29	n = 25	n = 24	n = 102
MABC overall percentile score, n (%)					
≥ P 16 normal	14 (58.3)*	19 (65.5)†	21 (84.0)	19 (79.2)	73 (71.6)*
P 6-P 15 borderline	7 (29.2)	7 (24.1)	1 (4.0)	3 (12.5)	18 (17.6)
≤ P 5 motor problem	3 (12.5)	3 (10.3)	3 (12.0)	2 (8.3)	11 (10.8)
Bruce SDS endurance time, mean (SD)§	(n = 22) -0.9 (1.3)#	(n = 22) -0.8 (1.1)#	(n = 19) 0.2 (1.3)	(n = 19) -0.3 (1.3)	(n = 82) -0.5 (1.3)#
Advise pediatric physiotherapy at home, n (%)	5 (20.8)	8 (27.6)	4 (16.0)	1 (4.2)	18 (17.6)

* *Chi Square: p < 0.01 (comparison to the percentage expected)*
† *Chi Square: p < 0.05 (comparison to the percentage expected)*
§ *Kruskal Wallis: p < 0.05 (difference between groups)*
# *One sample Test : p < 0.01 (SDS significant below zero)*

Only one EA-patient with a ventricular septal defect was classified as having a definite motor problem, the other nine children with cardiac malformations performed within the normal range.

Fourteen of the 102 tested children (13.7%) received pediatric physiotherapy (CDH n = 3, EA n = 7, SIA n = 4). Seven of them scored < P5, one between P5 and P15, and the other six scored within normal range. For 18 patients it was thought advisable to start (n = 6) or to continue (n = 12) pediatric physiotherapy at home. These 18 children scored significantly worse on the MABC than did the other 84 children ($p < 0.001$).

Discussion

This study describes standardized motor-function assessment and assessment of exercise capacity in 5-year-old children born with major anatomical congenital anomalies (CA). Motor-function was found normal for 73 of the 102 tested children (71.6%). This proportion is significantly lower than expected from the normative scores. We identified differences in the sub-scores of the MABC depending on primary diagnosis. Children with EA have more problems with ball skills and balance; those with CDH have problems with ball skills. The higher the number of additional congenital anomalies, the greater the impairment of motor-function performance is. Exercise capacity was analyzed in 82 children; they performed worse than expected on the basis of normative scores. Poor performance in CDH and EA patients was responsible for this outcome.

We excluded patients with syndromal abnormalities, and those with neurological impairment. Although neurological evaluation did not reveal serious problems in the

remaining study population and cerebral ultrasound examination within the first months showed slight abnormalities in the minority of patients (n = 4), minor neurological dysfunction with clumsy motor behavior may be present and explain –at least to some extent– our results. Children with major anatomical CA are at risk for several perinatal risk factors reported to be associated with minor neurological dysfunction: intrauterine growth retardation, mild to moderate perinatal asphyxia, and prenatal stress resulting from psychological stress of the mother.[15]

Holm et al[4] showed that eight-year-olds born with a complex congenital heart disease have lower MABC TIS and sub-scores than their healthy age- and sex-matched controls. The proportion of children with cardiac malformations in our study was low, and the majority of these malformations were not complex. This may explain that we found higher scores than in Holm's paper.

Next to TIS and sub-test scores of the MABC, maximal exercise performance was also assessed. Maximal exercise capacity was impaired in patients with CDH and EA. This is in line with previous studies by Zaccara et al. in CDH patients and in patients who were operated for tracheoesophageal fistulas.[16,17] Several authors have reported on the relationship between exercise capacity and motor competence. Haga et al.[18] established exercise capacity in 9- and 10-year-old children, showing a significant correlation between the TIS of the MABC and exercise capacity. This may be explained by physical activity levels; exercise capacity results from the degree and intensity of a child's physical activity over time.[19] In the same vein, one can also argue that motor competence is a consequence of the level of physical activity, e.g. the more time spent practicing motor skills, the more opportunity there is for better motor performance. We assume that CDH and EA patients, with high respiratory and gastrointestinal morbidity during the first years, get little physical activity and have few opportunities to practice gross motor skills. This may explain the lower percentile scores in these groups, and the differences in motor-function profiles (poorer ball skills and balance, but good performance at manual dexterity). As their physical activity is lower and their gross motor-function is impaired they are at risk for decreased maximal exercise tolerance. And, in a study of Majaesic et al., especially children with CDH, and those treated with ECMO had poor pulmonary outcome at 8 years of age. These authors assume that respiratory morbidity impairs maximal exercise tolerance.[20] Most children with SIA and AWD have few problems beyond the first few months of life,[21] and may have more opportunities for physical activity and hence for improving motor competence. In addition, undetectable neurological damage, perhaps secondary to minor neurovascular problems during surgery or veno-arterial ECMO-treatment cannot be ruled out. This assumption is supported by the fact that EA patients underwent the highest number of surgical interventions and only CDH patients were treated with ECMO.

Another factor that may contribute to decreased physical activity is parental reluctance to stimulate their child too much of fear for physical problems. CDH and EA patients both suffer from pulmonary morbidity and respiratory distress may easily occur after physical activity. Holm and Bjarnason[4,5] reported a similar parental protection in children with cardiac malformations.

A limitation of our study is that in this single centre study, per subgroup, the number of subjects studied was small, which makes it difficult to draw hard conclusions. Comparison of baseline characteristics of patients who were lost to follow-up with the participants revealed that only for CDH patients a possible selection bias might have occurred because participants were hospitalized longer. However, there were no differences regarding the need for extracorporeal membrane oxygenation (ECMO) and duration of ventilatory support. Other possible limitations are the lacking of more detailed neurological examination focused on minor coordination and balance dysfunctions, and a potential selection bias because of the fact that more children of non-Dutch origin were lost to follow-up. However, in children with CA motor-function development up till 2 years was not influenced by ethnic origin.[2]

Early identification of children at risk for developmental motor problems is very important. Predictive models as recently presented for preterms may be of great interest.[22] Studies in children born prematurely have shown that assessment of motor development by a pediatrician alone is insufficient and that standardized tests are needed.[23] Since motor problems do not disappear spontaneously[6] and may be associated with learning disabilities and behavioral problems[15] long-term multidisciplinary follow-up and adequate intervention when necessary are important. The use of validated standardized assessment instruments is of great help in this respect.

In addition, adequate and repeated instructions about positive effects of physical activity may help parents to be less overprotective.

CONCLUSION

Children with CA are at risk for delayed motor-function performance and exercise capacity, especially those with CDH and EA and those with additional anomalies associated with longer hospitalizations and multiple surgical interventions.

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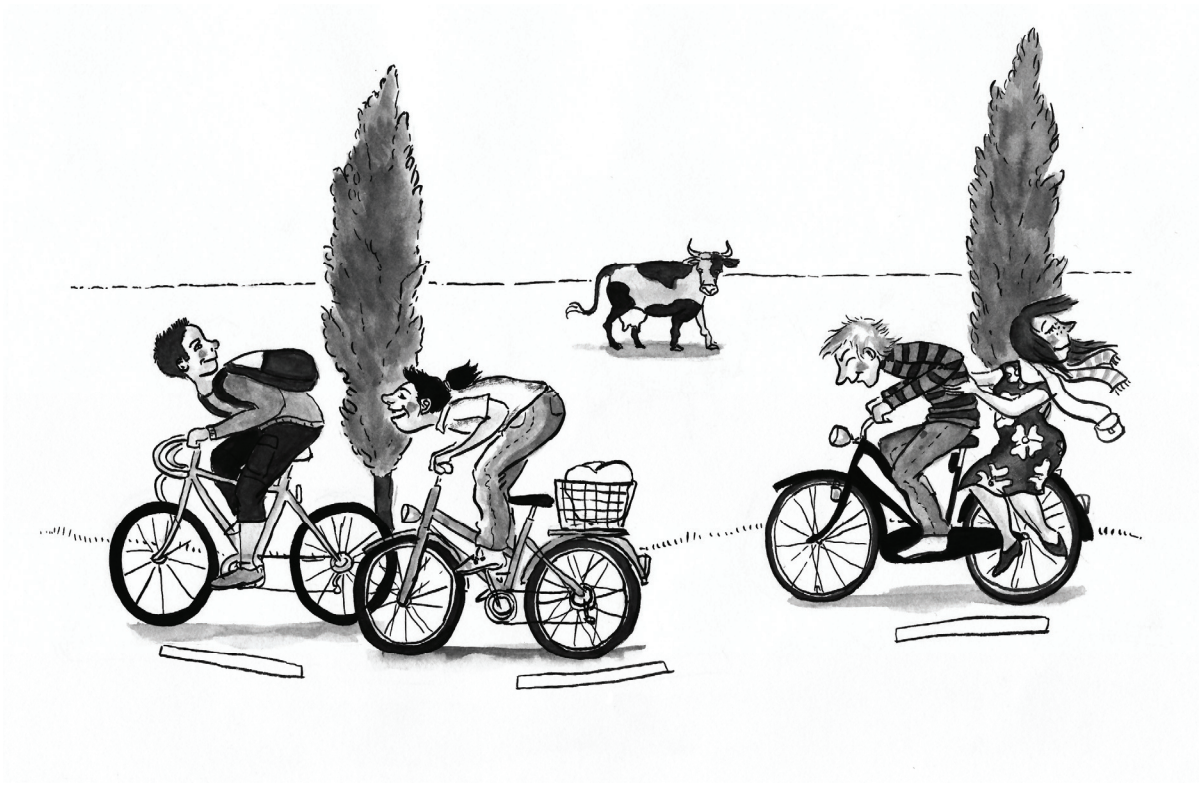
Chapter 5

Exercise capacity, fatigue, and level of physical activity in young adults with congenital diaphragmatic hernia



ABSTRACT

Rationale

Limited information is available on long-term outcome of exercise capacity, severity of fatigue, and level of physical activity in young adults born with congenital diaphragmatic hernia (CDH).

Objectives

To determine these long-term effects in adulthood in CDH patients and in term born age-matched controls without CDH and lung hypoplasia, who underwent similar neonatal intensive care treatment.

Methods and measurements

We studied 27 young adults (mean (SD) age: 26.8 years (2.9)) with CDH and 30 age-matched controls. Exercise capacity was evaluated with a bicycle ergometer test, severity of fatigue with the Fatigue Severity Scale. In 15 CDH patients and 13 controls level of physical activity was measured with an accelerometry-based activity monitor.

Main results

Mean VO_2peak (ml/min/kg) in both groups was significantly lower than normal (CDH 84.0% and controls 84.7% predicted; $p < 0.001$ in both groups compared to normal reference). This also applied to mean VO_2peak (ml/min) in CDH patients (89.7% predicted; $p = 0.011$).

No significant differences between the groups were found in exercise capacity, severity of fatigue, and level of physical activity. In CDH patients, severity of fatigue was negatively related with VO_2peak (ml/min/kg) % predicted ($R = -0.49$; $p = 0.01$).

Conclusions

Both CDH patients and age-matched controls have reduced exercise capacity. We found only few differences between both groups, indicating that not only residual sequelae of CDH but also therapeutic modalities for neonatal respiratory insufficiency and intensive care treatment contributed to the outcome of CDH in adulthood.

INTRODUCTION

Congenital diaphragmatic hernia (CDH) combines a developmental defect of the diaphragm with pulmonary hypoplasia, abnormal pulmonary vascular development and vaso-reactivity.[1] Increasingly the focus of interest has shifted from mortality to morbidity.[2] Several cross-sectional studies, mainly in young and adolescent CDH patients, have documented a range of long-term complications, such as mild airway obstruction;[3] increased bronchial responsiveness;[4] progressive ventilation/perfusion mismatches;[5] cognitive, emotional and behavioral problems;[6] chest wall deformities;[4,7] gastro-oesophageal reflux;[8] and motor problems.[9] Zaccara et al[10] described reduced maximal oxygen uptake (VO_2max) during exercise performance in 15 children operated for CDH (mean age 11.3 years, range 6 - 19 years), while normal or nearly normal exercise performance was described by Marven[11] (mean age participants 11.5 years, range 7 - 17 years) and Trachsel[7] (mean (SD) age participants 13.2 (2.2) years). Participants studied by Marven et al had a lower perception of their own fitness and lower enjoyment of exercise than healthy age-matched controls.

In 1997 we reported pulmonary sequelae in 38 children (median age 11.7 years, range 7.4 - 17.6 years) with CDH and in 65 age-matched controls without CDH who underwent similar neonatal intensive care treatment. All patients had been treated in an era before extracorporeal membrane oxygenation (ECMO), nitric oxide (NO) administration and high frequency ventilation (HFO) were available. We found increased bronchial responsiveness, normal carbon monoxide diffusion capacity (DL_{CO}) and mild airway obstruction in both groups with more peripheral airway obstruction in CDH patients.[4] We did not evaluate maximal exercise capacity in our former study.

Apart from findings of Peetsold et al[3] -i.e. normal exercise capacity and gas exchange parameters in 12 adult survivors of CDH- little is known about exercise capacity and health status in adult patients who underwent surgical repair of CDH in the neonatal period. Moreover it is unclear whether and to what extend CDH influences severity of fatigue and level of physical activity.

The aims of the present study therefore were:

- to assess exercise capacity, severity of fatigue, and level of physical activity in our previously studied cohort of CDH survivors and in their age-matched controls, who underwent similar neonatal intensive care treatment;
- to investigate correlations between exercise capacity and perinatal characteristics, and between exercise capacity and characteristics at young adult age in our previously studied cohort of CDH survivors.

METHODS

Participants

Inclusion criteria: all patients (40 CDH and 65 controls), who participated in the study of IJsselstijn et al.[4] The control patients had been matched as best as possible for age at follow-up, gestational age, birth weight, duration of artificial ventilation, duration of supplemental oxygen, and sex. We screened all participants with the Physical Activity Readiness Questionnaire (PAR-Q)[12,13] and participants had to be clinically stable for at least 3 weeks. Exclusion criterion: serious comorbidity. The Erasmus MC Medical Ethical Review Board approved the study and we obtained written informed consent from all participants.

Procedure

Any medication for pulmonary disease was discontinued 24 hours prior to the tests. On one and the same day, medical assessment and lung function tests were performed between 9 and 11.30 am; a maximal exercise test between 12 am and 2 pm. Participants completed questionnaires on this day as well.

Medical assessment

Height (cm) and weight (kg) were measured. Sports participation was classified into absent (no sports participation), moderate (< 4 times a week) or intense (≥ 4 times a week). Paid employment was understood as having at least 12 hours of paid employment weekly. Smoking was classified as "yes" or "no", and if yes was quantified in terms of "pack years": (number of cigarettes smoked per day x number of years smoked)/20 (1 pack has 20 cigarettes). Presence or absence of scoliosis was determined by a standardized physical examination, and if present was classified into mild or severe (referral to orthopaedic surgeon required).

Spirometry

Spirometry was performed with a dry rolling seal spirometer (Jaeger, Wurzberg, Germany) according to ERS criteria.[14] To assess potential airway obstruction and to prevent exercise-induced bronchoconstriction, spirometry was repeated after inhalation of 12 mcg of formoterol. Forced expiratory volume in 1 s (FEV_1) and FEV_1/forced vital capacity (FVC) were expressed as Z-scores.[15] To study relationship between lung function and exercise capacity, we only analysed spirometric data after bronchodilation. In addition we measured carbon monoxide diffusion capacity (DL_{CO}) using a single-breath method. Reference values for DL_{CO} and DL_{CO} corrected for alveolair volume (DL_{CO}/V_A) were based on the reference equations according to Stam et al.[16] For males: DL_{CO} ($\mu mol.s^{-1}.kPa^{-1}$) = 271 - (2.1 x age) (SD 25); for females: DL_{CO} = 187 - (1.3 x age) (SD 19). For males and females: DL_{CO}/V_A ($\mu mol.s^{-1}.kPa^{-1}.L^{-1}$) = 31.5 - (0.17 x age) (SD 3.4).

Exercise testing

Maximal cardiopulmonary exercise testing (CPET) was performed on an electrically braked cycle ergometer according to ATS/ACCP guidelines.[17] Resistance was increased every min with a variable load according to recommendations of Wasserman.[18] Pedal frequency was maintained between 50 - 70 revolutions/min with the aid of a visual pedal rate indicator. Heart rate before and during the test was monitored with a pulse Oximeter (MARS (motion artifact reduction system), type 2001, Respironics Novametrix, Murrysville (PA)). Respiratory gas was monitored on a breath-by-breath basis using a Jaeger Oxycon Pro (Care Fusion, Houten, The Netherlands). Cardio respiratory fitness was defined as the mean oxygen uptake during the last 30 s of exercise (VO_2peak: in ml/min and in ml/min/kg). The ventilatory anaerobic threshold (VAT, expressed as percentage of the pred VO_2peak) was estimated by the ventilatory equivalent method, when the ventilatory equivalents for oxygen uptake (VE/VO_2) and end tidal oxygen ($PetO_2$) increased while the ventilatory equivalents for carbon dioxide output (VE/VCO_2) and end tidal carbon dioxide ($PetCO_2$) remained stable.[18,19] Peak workload (W_{peak}) was defined as the mean highest workload maintained during 1 min. The CPET was considered to be maximal if one or more of the following conditions were met: the maximal pred heart rate was achieved (> 80% of pred; pred = 220 bpm - age (years)), respiratory exchange ratio (RER = ratio of VCO_2/VO_2) > 1.15, or exhaustion of the participant.[17] The Borg category scale for rating perceived exertion[20] measured subjective strain immediately after the final stage of the exercise test. Participants rated strenuousness of the test on a scale from 0 (no effort at all) to 10 (maximal effort). VO_2peak in ml/min/kg and VO_2peak in ml/min were calculated as percentage of the pred VO_2max by Shvartz and Reibold.[21] We analyzed plasma lactate concentrations at rest and 3 min after peak exercise. After blood withdrawal from a peripheral vein, one volume of heparin blood was collected in a tube containing one volume ice-cold 1 M perchloric acid, within 60 s of withdrawal. The tube was mixed and left on ice another 10 min before centrifugation for 15 min at 5500 rpm. The supernatant was stored at -20 °C. Lactate was measured in the supernatant on a Cobas c501 analyzer (Roche Diagnostics, Almere, The Netherlands).[22]

Questionnaires

To assess the severity of fatigue experienced in daily life we used the Fatigue Severity Scale (FSS).[23] "Fatigue" was defined as a score of > 1 SD (FSS ≥ 4) and "severe fatigue" as a score of > 2 SD (FSS ≥ 5.1) above the mean score in healthy individuals.[24] The Dutch Life Habits Questionnaire (LIFE-H 3.0) was used to evaluate functioning in daily activity and social participation. Scores for the two sub-domains (daily activity and social roles) and the Life Habit total score were calculated. A score < 8 indicated difficulty in performance.[25] Health status was measured with the Short Form (SF) 36, which consists of 36 questions organized into eight domains.[26] Two summary scores can be derived: physical health and mental health. SD scores were calculated using Dutch population norms adjusted for age (25 - 34 years).[27]

Level of physical activity

The level of physical activity was measured with an accelerometry-based activity monitor (AM) during two consecutive weekdays (48 hours). The AM is an ambulatory device that objectively measures mobility related activities of the human body by detecting the accelerations of the torso, the upper left leg and the upper right leg. Detailed information on methodology and validity has been published previously.[28] We analyzed the level of daily physical activity by 1] the duration of dynamic activities (composite measure of the separately detected activities walking, cycling, general non-cyclic movement) as a percentage of a 24-h period; 2] mean motility (in gravitational acceleration), representing both duration and intensity of daily physical activity; and 3] motility during walking (in gravitational acceleration), representing walking speed. Data were compared with those of 45 healthy subjects (retrieved from a database of the Department of Rehabilitation Medicine and Physical Therapy of our institution).

Data analysis

Body mass index (BMI) was calculated and the Dutch Growth Analyser, version 3.0 (Dutch Growth Foundation, Rotterdam, the Netherlands) served to calculate SDS for height on the basis of Dutch reference values published in 2000.[29] Mann Whitney U tests were used to test differences in perinatal characteristics between participants and non-participants. One-sample t-tests were used to test whether the mean SDS height, FEV_1, FEV_1/FVC, DL_{CO}, DL_{CO}/V_A, and % pred VO_2peak (in ml/min/kg and in ml/min) within both groups were different from those of the norm population. Data of normally distributed variables were compared between CDH patients and matched controls using Mixed Model ANOVA taking account of the paring of individuals. Other data of CDH patients and matched controls were compared with Wilcoxon's signed rank tests or Mc Nemar's tests. In case two controls were available for one CDH patient, the mean value of two matched controls was used in this analysis. For CDH patients, we analyzed the following components to investigate if they had a significant association with the VO_2peak (in ml/min/kg) % pred: days of neonatal ventilatory support, days of neonatal supplementary oxygen, SDS height at follow-up, SDS FEV_1, SDS FEV_1/FVC, SDS DL_{CO}, SDS DL_{CO}/V_A, smoking habits, sports participation, paid employment, FSS score, Life-H total score, Life-H daily activities, Life-H social participation, SF36 SD physical health, and SF36 SD mental health using ANOVA. Data of the AM measurement were calculated per day (24-h period) and averaged over the two measurements days (since there was no difference between the first and the second 24-h period). Univariate analysis of variance served to compare data of AM measurements of CDH patients with those of control patients and those of healthy subjects. For continuous parameters with a lognormal distribution (days of neonatal ventilatory support, days of neonatal supplementary oxygen, duration of dynamic activities, mean motility) we transformed the data logarithmically in order to reduce the effect of outlying observations. Statistical

significance was accepted at two-tailed 5% level for all tests. Statistical analyses were performed using SPSS 15.0 for Windows.

RESULTS

All 40 CDH patients from the study of IJsselstijn et al[4] were approached. Eleven of these CDH patients refused participation, one patient was excluded because of acquired serious neurological comorbidity and one patient could not be traced. So, 27 CDH patients participated (68%). Their mean age was 26.8 years, range 21.5 - 34.1 years. For these 27 patients 48 matched controls were available; two other control patients had died (from causes unrelated to neonatal problems). Thirty of the 48 eligible control patients participated (63%) (see figure 1: flowchart). Mean age: 26.6 years, range: 21.5 - 30.9 years. Finally 18 CDH patients each had one control patient and 6 CDH patients each had 2 control patients. Control patients were not available for the 3 remaining CDH patients. The 30 control patients had needed neonatal intensive care for: meconium aspiration (n = 12), persistent fetal circulation (n = 5), respiratory distress syndrome (n = 5), asphyxia (n = 4), pneumonia (n = 3), and sepsis (n = 1). There were no significant differences in perinatal characteristics between participants and non-participants, neither in the CDH group nor in the group of their age-matched controls (data not shown).

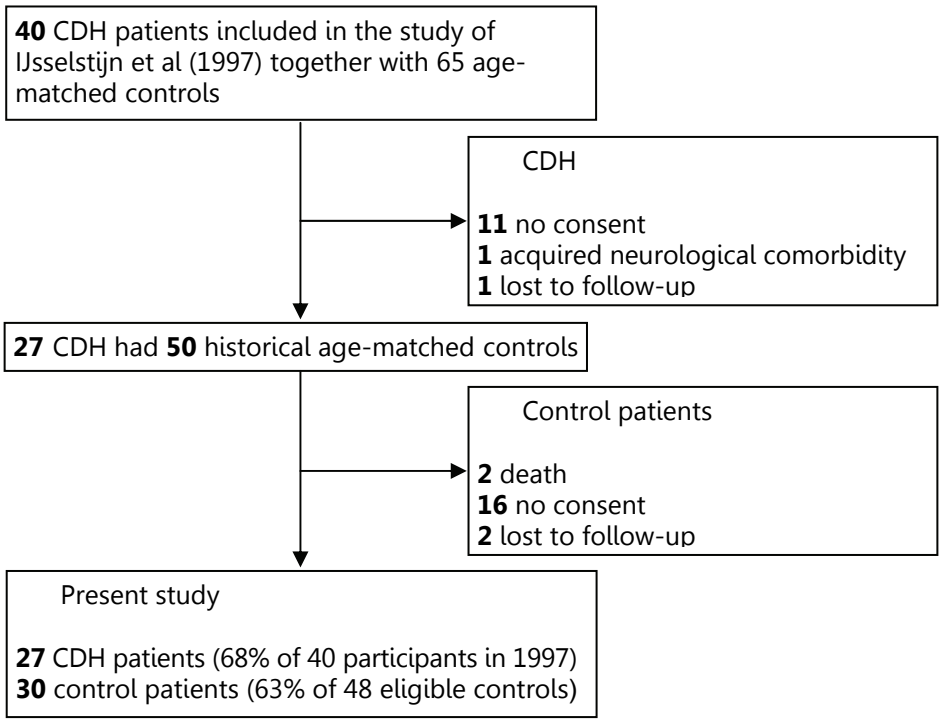


Figure 1 *Flowchart*

At examination, mean height of the CDH survivors was significantly lower as compared to their age-matched controls ($p < 0.01$, between groups p value). In CDH patients mean SDS FEV_1, SDS FEV_1/FVC, SDS DL_{CO} and SDS DL_{CO}/V_A were significantly below zero ($p < 0.01$, within groups one sample t-test). In the control patients only the mean SDS DL_{CO} was significantly below zero. Mean SD FEV_1/FVC in CDH patients was significantly lower than in controls ($p = 0.008$, between groups p value). Scoliosis was seen only in CDH patients (Table 1). SDS FEV_1 in CDH patients with scoliosis was lower than in CDH patients without scoliosis ($p = 0.02$, Mann Whitney U test).

Table 1 *Characteristics of participants*

	CDH	**Control patients**
	n = 27	n = 30
Male; n (%)	16 (59)	20 (67)
Birth weight, kg; mean (SD)	3.2 (0.6)	3.0 (0.6)
Ventilatory support, days; median (range)	4 (0 - 142)	4.5 (0 - 25)
Supplementary oxygen, days; median (range)	6 (0 - 60)	5 (0 - 19)
Age at examination, years; mean (SD)	26.8 (2.9)	26.6 (2.4)
BMI; mean (SD)	23.8 (4.4)	24.3 (3.8)
SDS length; mean (SD) *	-0.9 (1.1)	0.0 (0.9)
Lung function indices		
SDS FEV_1; mean (SD)	-1.4 (1.6)†	-0.4 (1.7)
SDS FEV_1/FVC; mean (SD) ‡	-0.9 (1.2)†	0.0 (1.2)
SDS DL_{CO}; mean (SD)	-1.5 (1.1)†	-1.1 (1.0)†
SDS DL_{CO}/V_A; mean (SD)	-0.5 (0.7)†	-0.2 (0.8)
Scoliosis; n (%)		
mild	5 (19)	0 (0)
severe	2 (7)	0 (0)
Smoking;		
yes; n (%)	12 (44)	8 (27)
pack years of smokers: median (range)	10.4 (3.5 - 30.0)	8.8 (0.1 - 22.5)
Sports participation; n (%)		
no	14 (52)	10 (33)
1 - 4 times weekly	6 (22)	14 (47)
≥4 times weekly	7 (26)	6 (20)
Paid employment; n (%)		
no	3 (11)	2 (7)
> 12 hours weekly	24 (89)	28 (93)

CDH: congenital diaphragmatic hernia, BMI: body mass index, FEV_1: forced expiratory volume in 1 s, FVC: forced vital capacity, DL_{CO}: diffusion capacity carbon monoxide, VA: alveolar volume
* *between groups p value = 0.002*
‡ *between groups p value = 0.008*
† *within groups one sample t-test mean value significantly different from 0: p < 0.01*

Three patients (1 CDH and 2 control patients) did not perform CPET: the CDH patient had unstable diabetes and the 2 controls showed motor skill disorders. Technical problems led to unreliable data in 1 control patient. Thus, reliable exercise data were obtained in 53 patients (26 CDH and 27 control patients). Median workload (Wpeak) was 150 W (range 113 - 180 W) and 250 W (range 120 - 338 W) in the 11 females and the 15 men of the CDH group, respectively. This was 180 W (range 135 - 225 W) and 281 W (range 210 - 338 W) in the 7 females and 20 men in the control group. Mean VO_2peak (ml/min/kg) in both groups was significantly lower than predicted. This also applied to VO_2peak (ml/min) in CDH patients. Mean (SD) HR at maximal performance was 180.3 (13.8) bpm in CDH patients (93.3% pred) and 183.5 (10.5) bpm in the control group (94.8% pred). No differences were observed between groups in VO_2peak, VAT, RER, heart rate at peak performance and Borg score. Peripheral venous lactate concentration was similar in both groups at rest. Differences between concentrations 3 min after peak exercise and at rest were also similar in both groups (Table 2).

Table 2 *Results*

	CDH	**Control patients**	**Between groups p-value**
Exercise test	n = 26	n = 27	
VO_2peak ml/min, % pred	89.7 (19.3)*	96.6 (15.8)	0.10
VO_2peak (corrected for kg) ml/min/kg, % pred	84.0 (16.1)†	84.7 (14.4)†	0.87
VAT (% of the predicted VO_2peak ml/min)	56.4 (13.5)	60.5 (16.4)	0.29
Respiratory exchange ratio	1.2 (0.1)	1.2 (0.1)	0.09
Heart rate (bpm) at peak exercise	180.3 (13.8)	183.5 (10.5)	0.34
Borg score	8.7 (1.1)	8.7 (1.3)	0.90
Venous lactate concentration	n = 20	n = 22	
Rest (plasma; mmol .l ¯¹)	1.0 (0.4)	1.0 (0.4)	0.66
Peak (plasma; mmol.l ¯¹)	8.0 (2.9)	8.7 (2.1)	0.29
Difference (peak-rest)	7.0 (2.9)	7.8 (2.1)	0.20
Questionnaires	n = 27	n = 30	
FSS Score ≥ 4; n (%)	10 (37)	4 (13)	0.14
Life-H Total Score < 8; n (%)	5 (19)	2 (7)	0.26
Life-H Daily Activities Score < 8; n (%)	5 (19)	1 (3)	0.03
Life-H Soc. Participation Score < 8; n (%)	6 (22)	4 (14)	0.42
SF 36 SDS physical health	0.0 (0.7)	-0.1 (0.7)	0.66
SF 36 SDS mental health	-0.2 (0.9)	-0.2 (1.0)	0.93

Data shown are number (%) of patients or mean (SD)
* *Within groups one sample t-test: mean value significantly different from 100: p = 0.011*
† *Within groups one sample t-test: mean value significantly different from 100: p < 0.001*

Questionnaires

Seven CDH patients (26%) and 1 control patient (3%) reported "fatigue" (FSS between 4 and 5.1), 3 CDH (11%) and 3 controls (10%) reported "severe fatigue" (FSS ≥ 5.1). Mean (SD) score on the FSS was 3.4 (1.5) for CDH patients; and 2.9 (1.2) for the control patients (p = 0.14, between groups p value). Overall, 5 patients (18.5%) in the CDH group and 1 (3.4%) in the control group had difficulties in daily activities as reported on the LIFE-H questionnaire (p = 0.03, between groups p value). Mean SDS physical and mental health scales of the SF 36 for both groups were not significantly different from zero (Table 2).

Correlations

In the group of CDH patients, ANOVA did not show significant associations between VO_2peak (ml/min/kg) % pred and the perinatal characteristics ventilatory support and supplementary oxygen, nor between VO_2peak (ml/min/kg) % pred and SDS height at follow-up, SDS FEV_1/FVC, SDS DL_{CO}, SDS DL_{CO}/V_A, smoking habits, paid employment, Life-H total score, Life-H daily activities, and SF 36 SD mental health (data not shown). SDS FEV_1, sports participation, Life-H social participation and SF 36 SD physical health were positively related with VO_2peak (ml/min/kg) % pred. The FSS score was negatively related with VO_2peak (ml/min/kg) % pred (Figure 2 and Table 3). In the group of control patients none of the above mentioned parameters was significantly associated with VO_2peak (ml/min/kg) % pred.

Level of physical activity

In 15 of the 27 CDH patients and 13 of the 30 controls the level of physical activity was measured with the AM. Logistic reasons resulted in refusal to participate by the other patients. There were no significant differences in perinatal characteristics between the 15 CDH participants and the 12 CDH non-participants. Also in the group controls we found no differences in perinatal characteristics between the 13 participants and the 17 non-participants (data not shown).

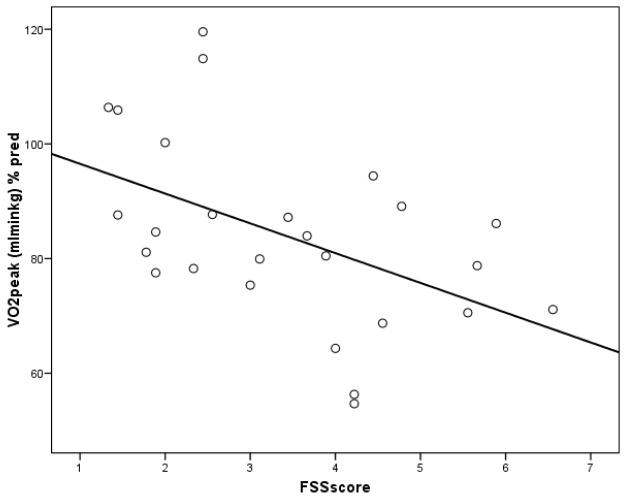


Figure 2 *Correlation between VO_2peak (ml/min/kg) % pred and score on the Fatigue Severity Scale (FSS) in CDH survivors. Pearson correlation coefficient: -0.49; p = 0.01*

Table 3 *Significant associations with VO_2peak (ml/min/kg) % pred in CDH patients (n = 27)*

	R	**p-value**
SDS FEV_1	0.40	0.04
FSS score	-0.44	0.01
SD SF 36 physical health	0.49	0.01
	Δ	**p-value**
Life habits total score (yes or no score ≥ 8)	18.6*	0.02

*R denotes Pearson correlation coefficient, * difference of means (score ≥ 8 minus score < 8), FEV_1:= forced expiratory volume in 1 sec, FSS = fatigue severity scale, SF 36 = Short Form 36*

We found a significant group and gender difference (p = 0.02 and 0.01 respectively) in duration of dynamic activities. Duration of dynamic activities was longer in women than in men. This difference was independent of the group effect (p = 0.36). Age was not associated with outcome. Duration of dynamic activities was longest in the group of age-matched controls (p = 0.02 in comparison with healthy subjects). No significant differences between the groups and no gender effects were found in mean motility and in motility during walking. Also age did not associate with outcome. (Table 4).

Table 4 *Physical activity as measured with the Activity Monitor*

	CDH	**control patients**	**healthy controls**
	n = 15	n = 13	n = 45
male / female	n = 8 / n = 7	n = 8 / n = 5	n = 19 / n = 26
age (yrs)	27 (22 - 31)	27 (24 - 31)	27 (19 - 38)
BMI (kg/m^2)	22.2 (18.3 - 29.0)	24.4 (18.6 - 31.0)	21.2 (16.8 - 28.0) (n = 38)
duration dynamic activities (% of measurement day) *	10.6 (7.0 - 32.7)	13.0 (6.0 - 29.5)	11.3 (5.0 - 21.6)
	n = 15	n = 13	n = 27
mean motility	0.025 (0.017 - 0.068)	0.026 (0.012 - 0.062)	0.027 (0.019 - 0.048)
	n = 15	n = 13	n = 31
motility during walking	0.188 (0.130 - 0.226)	0.167 (0.109 - 0.196)	0.171 (0.096 - 0.239)

Data are presented as median (range)
** Between groups difference (between age-matched controls and healthy controls): p value = 0.02*

DISCUSSION

The aim of the present study was to assess exercise capacity, severity of fatigue, and level of physical activity in our previously studied cohort of -in the mean time- young adults with CDH and in controls matched for age and similar neonatal intensive care treatment. Both CDH and control patients, showed diminished VO_2peak (in ml/min/kg)

in comparison with norm values reported by Shvartz and Reibold.[21] Thirty-seven % of the CDH patients reported fatigue as analyzed with the FSS. Regarding physical activity as assessed with the AM, we only found a significant difference in duration of dynamic activities between the age-matched controls and the healthy controls from our database, suggesting that the age-matched controls were more active than the healthy reference population. No significant differences between the groups were found in mean motility and in motility during walking. Exercise capacity, severity of fatigue and level of activity did not differ between the two groups, but more CDH patients than controls reported difficulties in daily activities. The LIFE-H total score and the sub score social participation did not differ between the groups. Scores on the SF 36 were similar in both groups and did not differ from the reference population.

We found no significant relationships between VO_2peak (ml/min/kg) and perinatal characteristics as ventilatory support and supplementary oxygen. Interestingly, from all lung function parameters, only the SDS FEV_1 correlated positively with VO_2peak (ml/min/kg). So, despite the fact that mean SDS FEV_1/FVC was significantly lower in CDH than in matched controls this did not result in worse exercise tolerance in CDH patients. Other factors than airway obstruction may play a role here. It has been speculated that reduced diffusion capacity of the lungs may explain a diminished exercise tolerance in CDH. However, this assumption is not supported by our data.

The association of the mean score on the FSS and the SDS of the physical scale of the SF 36 with the VO_2peak (ml/min/kg) suggests that diminished exercise tolerance can be suspected when patients complain of fatigue or physical impairment themselves. In those cases active intervention with recommendations about life-style and sports activities may be useful. To summarise our findings about maximal exercise capacity: we found similar levels of exercise capacity in CDH patients and controls, so it seems that not only residual consequences of CDH (as lung-hypoplasia) but also and perhaps mainly neonatal respiratory insufficiency and the ventilatory approach at that time contribute to the reduced exercise tolerance.

It could be argued that the reference values for VO_2peak may not be appropriate for our population, because they were collected a long time ago and in a different population. We chose the reference data by Shvartz and Reibold[21] for the following reasons: Shvartz and Reibold performed an extensive literature review of studies where VO_2max was directly measured in healthy untrained subjects in the USA, Canada and in 7 European countries. They included 98 samples of males and 43 samples of females, aged 6 - 75 years, in their review. We hold the view that of the available reference values those of Shvartz and Reibold are the best choice for our study population. The lack of more recent reference values and of a healthy control group besides our age-matched controls is a limitation of the present study and this might affect our estimation of the

magnitude by which VO_2 was reduced in both study groups. In 2007, Peetsold and colleagues[3] reported on exercise capacity in nine male and three female young adult survivors of CDH. Mean (SD) VO_2max % pred was 90.8% (18.9). As they used reference values of Wasserman and colleagues, direct comparison with our results is of no use.[18] Nevertheless, should we have used the same reference values, the mean (SD) VO_2peak % pred in the CDH patients would have been 96.3% (15.4); that in the control patients 98.3% (14.1). These values do not significantly differ between the two groups. Vrijlandt et al reported on exercise capacity in young Dutch adults born prematurely.[30] In their study exercise capacity of 41 pre-term born was compared to that of 47 healthy controls. Ex-preterms showed to have a lower exercise level and VO_2max than healthy controls when analyzed using the reference values of Wasserman et al.[18] Healthy controls, however, had a mean (SD) VO_2max % pred of 105 (20), so we may assume that values of Wasserman et al slightly underestimate exercise capacity of present-day healthy Dutch young adults.

Scoliosis was noted in CDH patients only. The prevalence was higher as previously described.[31,32] Possible reasons are that we also classified a mild scoliosis as scoliosis and that we did not perform radiographic measurement of Cobb's angle. We classified the scoliosis as mild in 5 of the 7 patients with scoliosis. Two patients with severe scoliosis (S-shaped scoliosis) were referred to an orthopaedic surgeon. In patients with a mild scoliosis the curvature of the spine was in 3 of the 5 patients to the left and in the other 2 patients to the right side. All patients with scoliosis had a left-sided CDH, so it can be wondered if the scoliosis was a result of long-term effects of CDH. On the other hand, even mild scoliosis was not observed in the matched control patients, and SDS FEV_1 in CDH patients with scoliosis was lower than in CDH patients without scoliosis ($p = 0.02$; Mann Whitney U test). So, we recommend early analysis of the spine from young age onwards.

A limitation of our study is that our patients were not evaluated for their cardiac performance. Therefore, we were not informed about ventilation/perfusion mismatch what is known to occur in these particular group of patients.[5] Riley and colleagues reported reduced exercise capacity in patients with PPH.[33] They found lower plasma lactate concentrations at peak exercise in their patients than in normal controls, suggesting ventilatory abnormalities with inefficient gas exchange because of impaired perfusion in the lungs of their patients. In our study venous lactate concentrations at rest and 3 min after peak exercise did not differ between the CDH and the control patients. Moreover, lactate concentrations after exercise correspond with the values measured by Riley et al in healthy controls. These observations suggest that PPH did not affect the results in our study population.

Recently we reported that exercise capacity of 5-year-old children with CDH was significantly below the norm.[34] In that study we used the Bruce treadmill protocol with recently established reference values for endurance time.[35] One can argue that the young adults evaluated in the present study had less residual pulmonary sequelae than younger children born with CDH in recent years. Survival rates of CDH patients, even those with more severe lung hypoplasia, have much improved owing to advancements in intensive care treatment. However, these might suffer from more severe residual pathology, and not necessarily do better than patients treated long ago. We, therefore, believe that the results of the present study confirm the necessity for intensive follow-up with recommendations about life-style, sports activities and physical activity level.

In conclusion, both CDH survivors and their matched controls showed to have diminished VO_2peak (ml/min/kg), suggesting that not only residual lung hypoplasia but also neonatal intensive care treatment contributes to our outcome. More CDH patients reported difficulties in their daily activities as estimated with the Life-H questionnaire.

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PART III

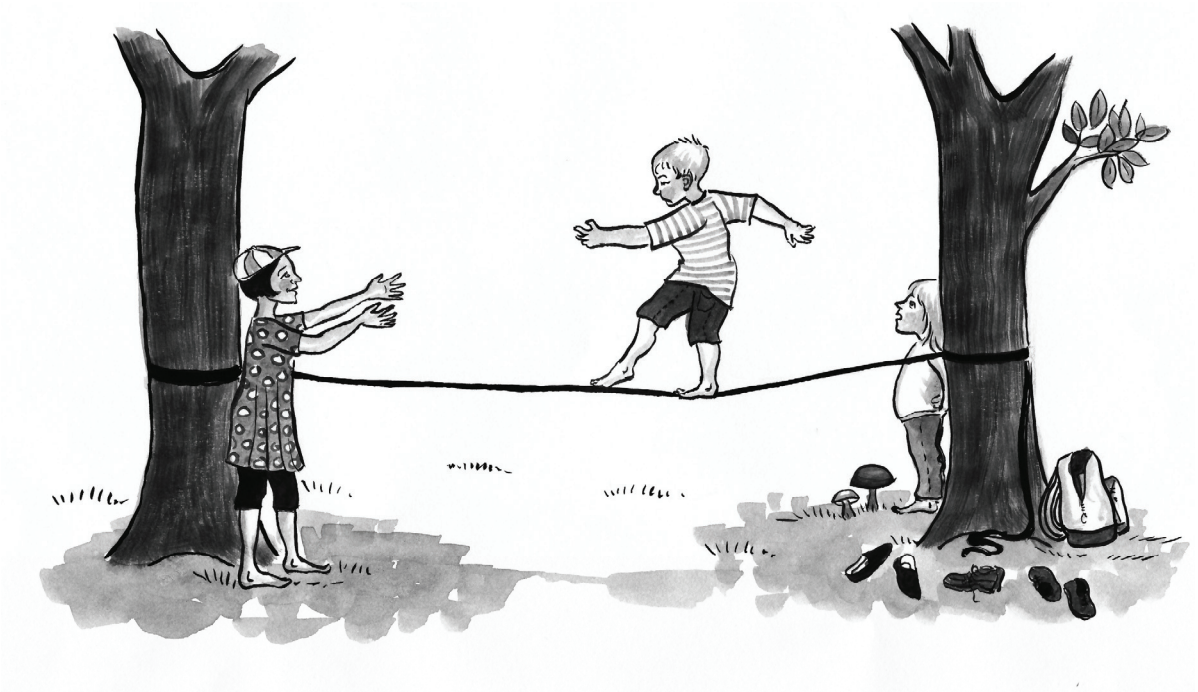
FOLLOW-UP ECMO

Chapter 6
Motor performance in five-year-old extracorporeal membrane oxygenation survivors; a population-based study
Maria W.G. Nijhuis-van der Sanden, Monique H.M. van der Cammen-van Zijp, Anjo J.W.M. Janssen, Jolanda J.C.M. Reuser, Petra Mazer, Arno F.J. van Heijst, Saskia J. Gischler, Dick Tibboel, Louis A.A. Kollée.
Critical Care, 2009;13:2:R 47.

Chapter 7
Deterioration of exercise capacity after neonatal extracorporeal membrane oxygenation
Monique H.M. van der Cammen-van Zijp, Saskia J. Gischler, Wim C.J. Hop, Johan C. de Jongste, Dick Tibboel, Hanneke IJsselstijn.
Provisionally accepted, European Respiratory Journal.

Chapter 6

Motor performance in five-year-old extracorporeal membrane oxygenation survivors: a population-based study



ABSTRACT

Introduction

Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is a cardio-pulmonary bypass technique to provide life support in acute reversible cardiorespiratory failure when conventional management is not successful. Most neonates receiving ECMO suffer from meconium aspiration syndrome (MAS), congenital diaphragmatic hernia (CDH), sepsis or persistent pulmonary hypertension (PPH). In five-year-old children who underwent VA-ECMO therapy as neonates, we assessed motor performance related to growth, intelligence and behaviour, and the association with the primary diagnosis.

Methods

In a prospective population-based study (n = 224) 174 five-year-old survivors born between 1993 and 2000 and treated in the two designated ECMO centres in the Netherlands (Radboud University Medical Centre Nijmegen and Sophia Children's Hospital, Erasmus MC - University Medical Center Rotterdam) were invited to undergo follow-up assessment including a paediatric assessment, the movement assessment battery for children (MABC), the revised Amsterdam intelligence test (RAKIT) and the child behaviour checklist (CBCL).

Results

Twenty-two percent of the children died before the age of five, 86% (n = 149) of the survivors were assessed. Normal development in all domains was found in 49% of children. Severe disabilities were present in 13%, and another 9% had impaired motor development combined with cognitive and/or behavioural problems. Chi-square tests showed adverse outcome in MABC scores ($p < 0.001$) compared with the reference population in children with CDH, sepsis and PPH, but not in children with MAS. Compared with the Dutch population height, body mass index (BMI) and weight for height were lower in the CDH group ($p < 0.001$). RAKIT and CBCL scores did not differ from the reference population. Total MABC scores, socioeconomic status, growth and CBCL scores were not related to each other, but negative motor outcome was related to lower intelligence quotient (IQ) scores ($r = 0.48$, $p < 0.001$).

Conclusions

The ECMO population is highly at risk for developmental problems, most prominently in the motor domain. Adverse outcome differs between the primary diagnosis groups. Objective evaluation of long-term developmental problems associated with this highly invasive technology is necessary to determine best evidence-based practice. The ideal follow-up programme requires an interdisciplinary team, the use of normal-referenced tests and an international consensus on timing and actual outcome measurements.

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is an effective treatment for respiratory failure in neonates suffering from meconium aspiration syndrome (MAS), congenital diaphragmatic hernia (CDH), sepsis or persistent pulmonary hypertension (PPH).

ECMO is associated with high survival rates (76%).[1,2] Nevertheless, survivors may suffer from long-term morbidity such as pulmonary dysfunction and cerebral damage, depending on the severity of primary illness and respiratory failure prior to ECMO and several factors during ECMO.[3-5] Prediction of long-term outcome after ECMO is not easy. Although neonatal brain injury tends to affect neuropsychological status at five years of age, evidence of functional recovery following brain injury has also been found.[6,7]

Most studies in ECMO survivors have so far focused on the health status at the age of one to three years.[1,3,8-10] Percentages of abnormal outcome in these studies differ, probably as a result of differences in study populations, assessment procedures and inclusion criteria. The range of morbidity widens after the first year of life when more precise assessment of cognition, coordination and behaviour is feasible. Long-term longitudinal follow-up would therefore seem essential for evaluating ECMO results.[11,12] Only a few studies have focused on neuromotor outcome from the age of four years and none of these analysed the relation between motor performance and health condition, cognition and behaviour.[12-14]

Previously, we presented the overall morbidity in Dutch ECMO survivors at the age of five years.[15] Six of the 98 children had major disabilities and 24 of the remaining 92 (26%) showed motor problems. The present study aims to evaluate in detail the characteristics of motor performance at five years of age in a larger Dutch ECMO population. We hypothesised that the motor performance profile is associated with the primary diagnosis. Moreover, we analysed the relations between motor performance problems, health status, cognitive and behavioural problems.

MATERIALS AND METHODS

Patients

A population who had received veno-arterial (VA)-ECMO support within 28 days of birth in either of the two ECMO centres in the Netherlands (Radboud University Medical Centre Nijmegen and Sophia Children's Hospital, Erasmus MC - University Medical Center Rotterdam) between January 1993 (Nijmegen) or 1996 (Rotterdam) and December 2000 (n = 224) and were alive at age five years (n = 174) were invited to undergo follow-up assessment (Figure 1). Neonatal data had been prospectively collected in an ECMO database.

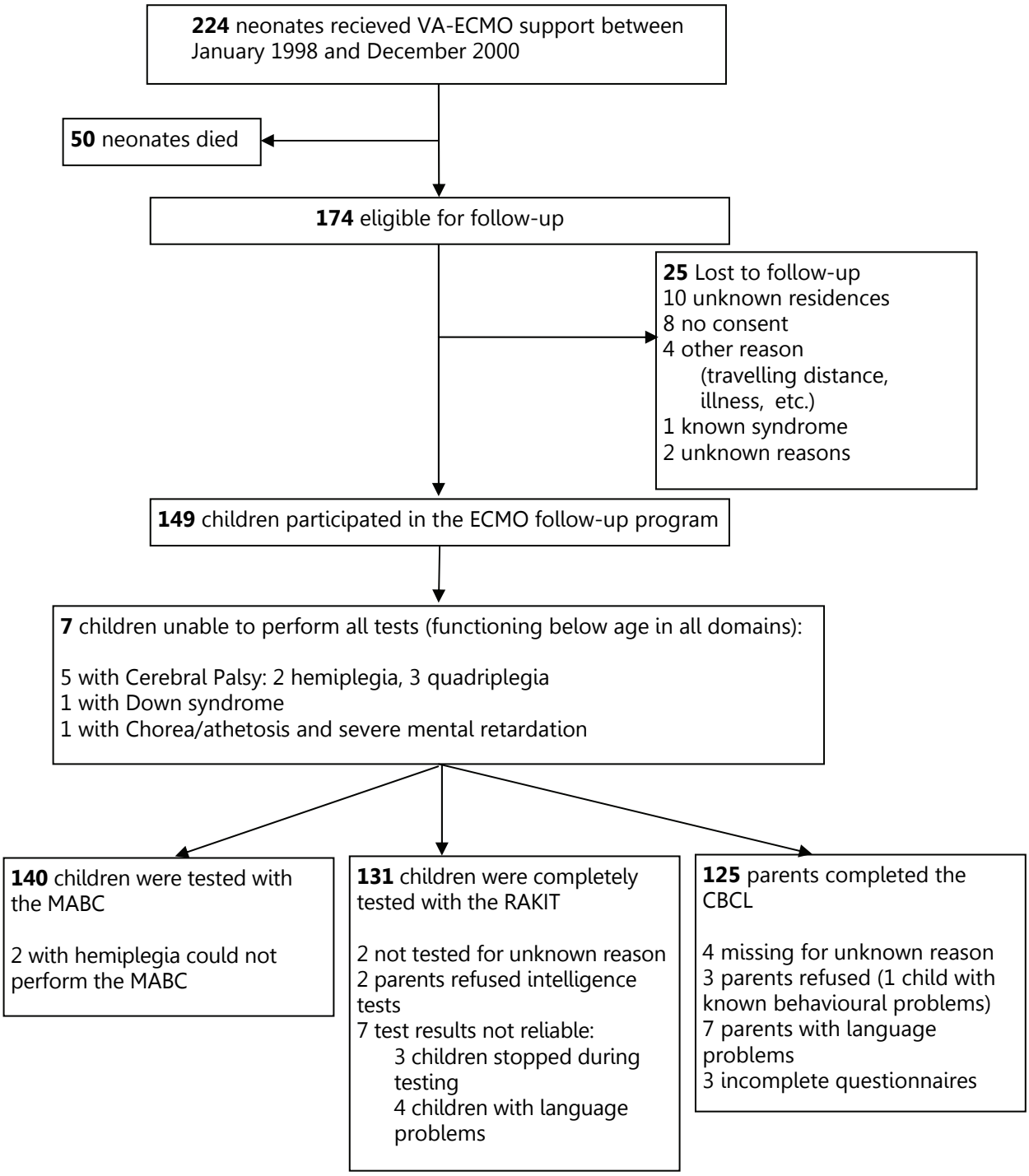


Figure 1 *Flowchart of children included in the VA-ECMO* follow-up programme at the age of five years. CBCL = child behaviour checklist; MABC = movement assessment battery for children; RAKIT = revised Amsterdam intelligence test; VA-ECMO = veno-arterial extracorporeal membrane oxygenation*

According to a national consensus on neonatal follow-up and the obligation to provide these data based on reports of the Dutch Ministry of Health, the assessment protocol is the Dutch standard of care in ECMO follow-up.[16,17] As a consequence no written informed consent from the parents was necessary. All parents were routinely informed about the longterm follow-up programme and use of anonymous data for study proposal in the neonatal period of life and again when they were invited for the

assessments at the age of five years. The ethical review boards in both Medical Centres were informed and agreed with the study.

Assessment protocol

Perinatal characteristics (Table 1) were recorded as submitted to the Extracorporeal Life Support Organization Registry.[2] A paediatrician, a paediatric physical therapist and a child psychologist assessed the five-year-olds during a single clinic visit.

Questionnaires

Parents completed a questionnaire evaluating the child's health status and employment and education of both parents. Three socioeconomic classes were defined using the standard Dutch profession classification.[18]

Paediatrician's assessment

The paediatrician performed a physical examination and took a medical history. Growth parameters were expressed in standard deviation (SD) scores using the Dutch Growth Analyser, version 3.0 (Dutch Growth Foundation, Rotterdam, the Netherlands).

Table 1 *Perinatal and extracorporeal membrane oxygenation (ECMO) characteristics of all survivors (n =174)*

	Infants not participating	**Infants in follow-up**
	n = 25	n = 149
Male/Female[1]: number	17/8	87/62
Birth weight (g)[2]: mean (SD)	3272 (560)	3367 (604)
Gestational age (weeks)[2]: mean (SD)	38.6 (2.3)	39.5 (2.0)
Primary diagnoses[1]:	number	number
Meconium aspiration syndrome	13	75
Congenital diaphragmatic hernia	4	32
Sepsis	4	16
Persistent pulmonary hypertension	2	25
Pulmonary hypoplasia	2	1
Duration of the ECMO (hours) [2]: mean (SD)	155 (57)	163 (64)
Neurological complications[1]: number	20 (5 missing)	120 (29 missing)
None	14	71
Haemorrhage	3	9
Cerebral infarction	0	6
Clinical epileptic insults	3	6
EEG epileptic insults	0	28

No differences were seen in perinatal characteristics between infants not participating and infants in follow-up; [1] Chi-square test: p > 0.05; [2] Student t-test: p > 0.05; EEG = electroencephalography; SD = standard deviation

Motor performance assessment

A paediatric physical therapist administered the movement assessment battery for children (MABC). It assesses skills related to motor functioning in daily life. The MABC has four age bands each with eight items grouped into three performance sections: manual dexterity (three items), ball skills (two items) and static and dynamic balance (three items). All items are scored quantitatively (duration in seconds or number of hits or errors). Section scores for manual dexterity, ball skills and static and dynamic balance, and a total impairment score can be calculated, with lower scores indicating better performance. Scores can be interpreted using the percentile normal data tables in the manual.[19,20] Scores above the 15th percentile are considered 'normal', between 5th and 15th percentile is considered 'borderline', and below the 5th percentile is 'definitively delayed'. A Dutch version of the test is available: interrater reliability ranges from 0.70 to 0.89, while test-retest reliability is 0.75.[19,20] The test is the most frequently used test to identify children with functional motor problems.[19,21,22]

Cognitive assessment and behaviour

A psychologist (assistant) assessed cognitive development with the short version of the revised Amsterdam intelligence test (RAKIT) – a reliable, validated, normal-referenced Dutch instrument containing six subtests.[23] Raw subtest scores are converted into standardised scores, which are then transformed into a short RAKIT intelligence quotient (IQ) with a mean of 100 and a SD of 15. 'Mild cognitive delay' was defined by a test result between -1 SD and -2 SD (IQ ≥ 70 and < 85), and 'definitive delay' by a test result lower than -2 SD (IQ < 70).

Behavioural outcome was assessed using the Dutch version of the child behaviour checklist (CBCL) for children aged 4 to 18 years.[24] The CBCL is a validated parental questionnaire and rates 113 problem behaviour items on a three-point scale (0 = not true, 1 = somewhat true, 2 = very true). The sum of all item scores results in a total score, which is recalculated into a percentile score. Scores of 59 or less are classified as 'within normal range', scores 60 to 63 as 'borderline' and scores 64 and above 'within clinical range'.

Data analysis

Independent t-tests or chi-square tests were used to test differences between the participating and non-participating children and to test whether the ECMO population differed significantly from the reference population in growth, motor performance, intelligence and behaviour. Two-sample t-tests and Mann Whitney U tests were used to examine the differences between diagnosis subgroups. Spearman correlations between motor performance scores and growth data, intelligence scores, behavioural scores and socioeconomic status were calculated. P values less than 0.05 were considered statistically significant. All analyses were performed using SPSS version 16.

RESULTS

As 25 of the 174 eligible children did not participate for various reasons (Figure 1), 149 (86%) children underwent follow-up assessment. The participating and non-participating groups did not differ in perinatal and ECMO characteristics (Table 1).

Patient characteristics at age five years are presented in Table 2. Mean and SD of height, SD of body mass index and SD of weight-for-height scores for the total sample were significantly lower than those for the Dutch reference population. Post-hoc analysis revealed that growth was within the normal range in the groups of children with sepsis and persistent pulmonary hypertension (PPH). In the group of children with meconium aspiration syndrome (MAS) only SD of height was lower than the normal range ($p < 0.03$), but in the congenital diaphragmatic hernia (CDH) population all three parameters were significantly lower ($p < 0.001$): 23 children with CDH (72%) had a weight for height lower than normal (50% < -1 SD, and 22% < -2 SD). Visual problems were rare (n = 8) and previously undetected in only one child. Hearing problems were also rare (n = 8) and previously undetected in three children.

Motor performance

Seven children were unable to partake in the assessments (Figure 1). Another two children with hemiparesis were not able to perform the MABC, so 140 children were tested with the MABC. Chi-square tests revealed more motor problems in these children than in the reference population ($p < 0.001$); 94 children (67% vs 85% expected) scored within the normal range, 23 children (16.5% vs 10% expected) were classified as 'borderline' and another 23 children (16.5% vs 5% expected) as 'definitively delayed'. Manual dexterity scores did not differ from those for the reference population. The majority of children (86%) were right-handed, as in the reference population. Proportions of children with ball skill problems were larger than in the reference population ($p < 0.001$): 82 normal (58% vs 85% expected), 36 borderline (26% vs 10% expected) and 22 definitively delayed (16% vs 5% expected). The same held true for balance skills ($p < 0.001$): 93 normal (66.5% vs 85% expected), 24 borderline (17% vs 10% expected) and 23 definitively delayed (16.5% vs 5% expected).

Motor performance profiles differed between the primary diagnosis groups, as shown in Figure 2. All test results for the one child with pulmonary hypoplasia were within the normal range (data not presented).

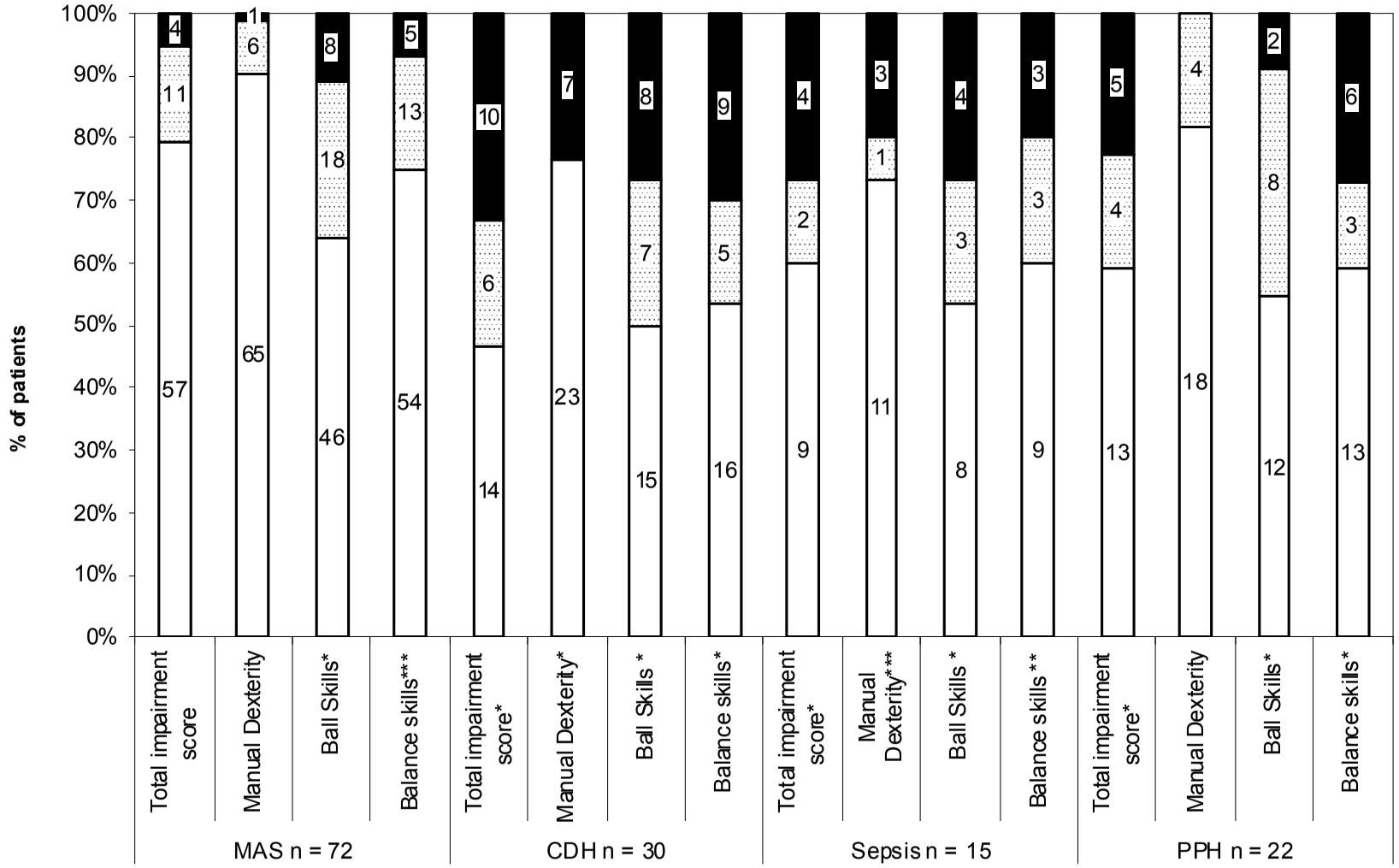


Figure 2 *MABC scores for the different groups; for each group TIS and sub-scores are shown.*
Normal range (> p 15, open bar); borderline range (p 6 – p 15, stippled bar); definitive motor problem (≤ p 5, black bar).
*Chi-square test (observed vs expected distribution): * p < 0.001; ** p < 0.002; *** p < 0.05.*
One child with pulmonary hypoplasia is not presented in the figure (all scores within the normal range). CDH = congenital diaphragmatic hernia; MAS = meconium aspiration syndrome; PPH = persistent pulmonary hypertension

Table 2 *Basic characteristics of the assessed group at 5 years of age (n = 149)*

Total group n = 149	
	mean (SD)
Age in months	62 (2.5)
Height SD score *	-0.4 (1.1)
Weight for height SD score **	-0.3 (1.4)
BMI SD score ***	-0.3 (1.4)
Motor performance percentile score (n = 140)	35.6 (28.4)
Intelligence score (n = 131)	99.7 (18.1)
Behavioural score (n = 125)	50.2 (9.9)
Socioeconomic status	number (%)
low	24 (16.1)
middle	65 (43.7)
high	30 (20.1)
unknown	30 (20.1)
Vision	number
normal	121
abnormal/ no glasses[1]	2
adequate correction with glasses	6
abnormal with glasses	0
unknown	20
Sense of hearing	number
normal	123
abnormal/ no hearing aid[1]	4
adequate correction with hearing aid	3
abnormal with hearing aid	1
unknown	18

** One sample t-test: p < 0.001; ** p < 0.05; *** p < 0.02*
[1] in 1 child with severe cerebral palsy correction was not possible
BMI = body mass index; SD = standard deviation

In the group of children with MAS, MABC total impairment scores and manual dexterity scores did not differ from the reference scores, although more problems with ball- and balance skills were found. Also in the PPH group, manual dexterity scores were not deviant. Nevertheless, MABC total impairment scores in this group were deviant on account of problems with ball- and balance skills. In both the CDH and sepsis group, motor performance was significantly lower in all domains. The CDH group scored significantly worse than the MAS group on MABC total impairment score ($Z = -2.4$, $p < 0.02$), balance skills ($Z = -2.8$, $p < 0.01$) and ball skills ($Z = -2.7$, $p < 0.01$), but not on manual dexterity. Differences between the other groups were not significant.

Intelligence and behavioural scores

One hundred and thirty-one children were assessed with the RAKIT (Figure 1). The IQ scores (mean = 99.7, SD = 18.1, n = 131) and the behavioural scores (mean = 50.2, SD = 9.9, n = 125) did not differ from those for the reference population ($p > 0.05$), neither in the total group nor in the primary diagnosis groups.

Motor performance relation with health status, cognition, behaviour and socioeconomic status

Table 3 shows outcomes for the total group and for the primary diagnosis groups including the children not tested because of already known severe disabilities. Mortality was highest in the CDH group (41.9%) and lowest in the MAS group (6.4%). The CDH group also showed lowest normal outcome in all domains (37.5%) versus 52.6% in the MAS group. Motor domain problems were the problems most frequently encountered in the total group (39.3%), in 22% of all cases combined with cognitive and behavioural problems. Only 12% of the children had cognitive or behavioural problems without motor problems.

None of the six children with cerebral infarction (four with MAS, one with CDH, one with PPH; Table 1) showed normal development. Four had severe problems in all three domains, one child had severe motor problems (hemiparesis) and one child had severe behavioural problems. Of the nine children with cerebral haemorrhage, four scored in the normal domain, three had abnormal development in all three domains, one child had borderline motor problems and one child combined motor and cognitive problems. Six children had clinical insults: four had normal outcome, one had severe cognitive problems and one had severe behavioural problems. Of the 28 children with neonatal seizures, shown on electroencephalography (EEG), only nine had normal development, 17 had motor problems (seven severe in more domains, three borderline motor combined with borderline cognitive and/or behavioural problems, seven borderline motor problems) and two had mild cognitive problems.

For the total group no significant relations were found between MABC total impairment scores, socioeconomic status or growth outcomes. Negative outcome on the MABC was significantly related to lower IQ-score ($r = 0.48$, $p < 0.001$), and significantly but weakly related to lower behavioural scores ($r = 0.18$, $p < 0.05$), although lower IQ-scores were significantly related to negative behavioural outcome ($r = 0.32$, $p < 0.001$) and SD height ($r = 0.23$, $p < 0.01$).

Table 3 *Outcome of neonatal ECMO intervention at the age of five years for the total group and specific diagnosis groups*

	Total group	**MAS**	**CDH**	**Sepsis**	**PPH**	**Other diagnosis**
	n = 224	n = 94	n = 62	n = 25	n = 34	n = 9
Children died, n (%)	50 (22.3)	6 (6.4)	26 (41.9)	5 (20.0)	7 (20.6)	6* (66.6)
Survivors	n = 174 24 missing	n = 88 12 missing	n = 36 4 missing	n = 20 4 missing	n = 27 2 missing	n = 3 2 missing
Survivors classified, n (%)	150 (100)	76[#] (100)	32 (100)	16 (100)	25 (100)	1 (100)
Children with severe problems in 2 or 3 domains, n (%)	20 (13.3)	6 (7.9)	5 (15.6)	4 (25.0)	5 (20.0)	
Children with mildly delayed motor development combined with mildly delayed cognitive development and/or behavioural development, n (%)	13 (8.7)	6 (7.9)	2 (6.2)	2 (12.5)	3 (12.0)	
Children with mildly delayed motor development and normal cognitive and behavioural development, n (%)	26 (17.3)	10 (13.2)	11 (34.4)	1 (6.2)	4 (16.0)	
Children with normal motor development, but mildly delayed cognitive or behavioural development, n (%)	18 (12.0)	14 (18.4)	2 (6.2)	2 (12.5)	0 (0)	
Children with normal development in three domains (MABC > p15; IQ > -1SD; CBCL > p25) , n (%)	73 (48.7)	40 (52.6)	12 (37.6)	7 (43.8)	13 (52.0)	1** (100)

* *diagnosis: 1 cystic adenomatoid malformation of the lung, 1 pulmonary hypoplasia, 2 pertussis, 1 idiopathic pulmonary hypertension, 1 acute respiratory distress syndrome*
** *diagnosis: pulmonary hypoplasia*
[#] *inclusive one child not in follow-up with a known syndrome*
CBCL = child behaviour checklist; CDH = congenital diaphragmatic hernia; ECMO = extracorporeal membrane oxygenation; IQ = intelligence quotient; MABC = movement assessment battery for children; MAS = meconium aspiration syndrome; PPH = persistent pulmonary hypertension; SD = standard deviation

DISCUSSION

This study presents five-year outcomes of a nationwide population of 224 neonates treated with VA-ECMO. Severe disabilities in all domains were found in 13.3% of the 174 surviving children. More than half of those with deviant motor performance outcome (26%) had cognitive problems and/or behavioural problems. Children with MAS or PPH had the best outcomes (52% normal). Children with CDH had the worst outcomes (only 37.5% normal in three domains), with more problems in the motor domain, combined with decreased growth. Although not significantly different, cognitive problems were most frequent in the MAS group (18.4%). Perinatal cerebral abnormalities and neonatal seizures as measured by EEG were highly related to deviant outcome.

In this study 25 children (14%) were lost to follow-up. These children did not differ in perinatal or ECMO characteristics, and the percentage of CDH children was somewhat lower and the number of non-native children was higher in the non-responder group. We cannot exclude that outcome will be somewhat worse as a result of disproportionately prevalent poorer outcome in the hard-to-trace subgroups.

The use of standardised tests allowed the comparison of this sample with an age-related reference population. We opted for the MABC because children may have motor performance problems even if the neurological examination is normal.[25] In the MABC assessment protocol children are provoked to perform age-related functional skills as fast and accurately as possible, comparable with the demands in daily life,[26] and these demands lace more load on the neurological system.

The literature contains a few earlier, similar studies. ECMO survivors in the UK were tested at ages four and seven years with standardised tests for cognitive and behavioural assessment, with the addition of MABC components at the age of seven years.[11,14]

Glass and colleagues[7,13] published two studies focusing on five-year outcome using the same protocols. Controls were recruited from a local paediatric practice. Both studies showed major disability in 17% of the ECMO patients (vs 13% in our study), motor disability was present in 5 to 6% of the children, and was related to cerebral palsy.

The incidence of severe disability in our study is comparable with that in the study by Glass and colleagues,[7,13] but somewhat higher than in the UK study group (2%). Motor performance problems seem to be more frequent in the UK study group (57% vs 33% in our study).[14] Although similar, the studies are hardly comparable because of different types of control groups, differences in test age, differences in decision rules (means and SD of MABC scores underlined the decisions in the UK study) and selection bias (a

selection of MABC test items in the UK study and tasks not related to daily activity in the study by Glass and colleagues). Therefore, we would like to advocate the use of normal-referenced tests to estimate motor performance in the same manner as IQ tests. Another explanation for different findings could be the difference in primary diagnoses in the above mentioned studies.

Functional motor problems interfere with the acquisition of everyday skills and cognitive and social-emotional development in preterm children.[27] In the present study motor problems often went together with cognitive and/or behavioural problems and total MABC scores were significantly related to IQ scores. Although we did not find lower IQ scores on the RAKIT, it should be borne in mind that the predominance of motor morbidity at age five years is likely in part to be due to the relatively young age of the cohort. It is conceivable that increased (subtle) cognitive morbidity will become more evident with age, when more academic and cognitive skills are required. Moreover, the short version of the RAKIT focuses on general intelligence and appears relatively insensitive to frontal lobe dysfunction. The UK studies support the hypothesis that motor problems influence the learning of cognitive skills in which movement planning is an important factor: at the age of four years, the ECMO children had specific problems with pattern construction and copying,[11] and at the age of seven years had problems with writing.[14] Glass and colleagues also found that the ECMO children had a two-fold risk for academic difficulties at school age and a higher rate of behavioural problems.[13]

Bulas and Glass reported that the severity of neonatal brain injury was predictive for neuromotor outcome at five years of age.[28] Still, they also found evidence of compensation following moderate or severe brain injury. A limitation of the present study is the absence of neuro-imaging data in all survivors. However, we found that clinical insults and neonatal seizures on EEG, besides cerebral infarction and haemorrhage, were predictive for adverse outcome. Future research should focus on the precise diagnostics of neonatal injuries and on the presence and influence of therapy programs and/or differences in parental care. These would gain insight into factors improving long-term outcome.

In the present study children born with severe pulmonary hypoplasia or large diaphragmatic defects were at higher risk for motor performance problems. They often also had cognitive and/or behavioural problems and growth scores below -1 SD, indicative of failure to thrive. Studies focusing on long-term morbidity in the CDH population are scarce. Hayward[29] and colleagues found a ventilation/perfusion mismatch and decreased postnatal lung growth in more than half of CDH patients at age one to two years, possibly caused by a limited catch-up growth in the postnatal period. Hamutcu[30] and colleagues found lung dysfunction (airway obstruction,

hyperinflation and hypoxia at rest) at the age of 9 to 13 years in 50 neonatal ECMO survivors with various primary diagnoses. They could not confirm differences in outcome related to primary diagnosis, possible as a result of the small number of children. Boykin and colleagues found abnormalities in baseline and post-exercise pulmonary functions in 10 to 15-year-old ECMO children with MAS as primary diagnosis.[31] In a multicentre, prospective study it was found that reduction in pulmonary function at eight years was linked to ECMO itself, CDH and small for gestational age.[32] Taken together, it can be concluded that although pulmonary dysfunction seems to be more serious in children with CDH, the ECMO treatment itself also increases risk of pulmonary problems. Future studies are needed into the relations between persistently reduced lung capacity, growth problems and conditional restrictions in motor activities in the ECMO population as a whole and the CDH population in particular.

In the absence of a matched control group it remains difficult to establish the extent to which ECMO treatment itself contributes to the outcome. The UK ECMO trial[1,3,14] did show a benefit for ECMO based on the primary outcome "death or severe disability". In a recent Cochrane review it was established that this is particularly true for infants with no specific problem of lung formation (CDH).[33] In a recent review focusing on the benefits of ECMO in infants with CDH, Morini and colleagues[34] concluded that ECMO leads to a reduction in mortality. However, in very severe CDH patients this may lead to long-term disability.[31,34] Unfortunately, at this moment most studies concentrate on the first years after ECMO and not on long-term outcome. The scattered data indicate substantial morbidity in long-term survivors of ECMO especially in CDH, including pulmonary damage and neurocognitive defects.

In this study we can confirm that the worst outcome was found in the CDH population: almost 42% of the children died as a neonate, 72% had growth problems, almost 16% had severe disabilities and another 6% had borderline problems in all domains, 34% had borderline motor problems and only 37.5% functioned in the normal domain. Although the outcome for children with MAS was much better, only 53% of the survivors functioned in the normal domain. In particular children with MAS seem to profit from ECMO intervention and less severe problems are present. The MAS children are the most healthy children in which neurological outcome is determined by an increased risk of perinatal and neonatal hypoxaemia in the first days of life. These children seem to have more diffuse problems in cerebral information processing such as diminished ball and balance skills, and relatively more cognitive and behavioural problems, also reported in children with mild or severe asphyxia during birth.

CONCLUSIONS

This study shows considerable morbidity in ECMO-treated survivors at age five years, which is not greatly different from that reported in previous publications. Decreased motor performance is the most frequent complication, often associated with problems in the cognitive and behavioural domains. The manual dexterity activities are less affected and ball skills and balance skills are most affected. These functional motor problems could interfere with the acquisition of everyday skills, and with later cognitive and social-emotional development. We, therefore, think that longer follow-up of children at risk of morbidity at age five years is required. In particular, the CDH group is at high risk because of failure to thrive. Moreover, perinatal cerebral complications, such as cerebral infarction, cerebral haemorrhage and neonatal seizures at the EEG, were predictive of an adverse outcome. Brain damage and pulmonary dysfunction seem to be important determinants. Precise registration of interventions and long-term outcomes are necessary for scientific evaluation and clinical management of the sequelae and the developmental problems. As local patient groups are usually small, national and international collaboration is recommended. We believe that a successful follow-up programme of the ECMO population should be structured in consultation with representatives from different disciplines such as paediatricians, paediatric physical therapists and psychologists. Improvement of long-term outcome requires not only insight into the primary diagnosis-related factors, the ECMO intervention related factors but also insight into factors stimulating recovery.

Key messages

- ECMO treatment decreases mortality; however, morbidity is high at age five years: 13% of the children were severely handicapped.
- Only 49% of the ECMO children showed normal outcomes in all domains, and motor performance problems were most often present, often combined with cognitive and behavioural problems.
- Manual dexterity activities are less affected and ball skills and balance skills are most affected.
- Morbidity in primary diagnosis groups differs: high morbidity in CDH children, lower in MAS and PPH children, and relatively high morbidity in the sepsis group.
- Precise registration of interventions and long-term outcomes are necessary for scientific evaluation and clinical management, and strong collaboration between disciplines and centres is required.

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Chapter 7

Deterioration of exercise capacity after neonatal extracorporeal membrane oxygenation

ABSTRACT

Extracorporeal membrane oxygenation (ECMO) provides life support in acute reversible cardio respiratory failure. Assessment of long-term morbidity is essential to confirm the survival advantage.

Objective of this study

To assess exercise capacity in the first 12 years of life after neonatal ECMO, and to evaluate the effect of primary diagnosis, lung function or perinatal characteristics on exercise capacity.

Patients and methods

A total of 120 children who as neonates underwent ECMO performed 191 reliable exercise tests according to the Bruce treadmill protocol at age 5, 8 and/or 12 years. Primary diagnoses: meconium aspiration syndrome (n = 66); congenital diaphragmatic hernia (n = 18); other diagnoses (n = 36).

Results

At ages 5, 8 and 12 years, ANOVA resulted in mean (± SE) SDS endurance time on the treadmill of -0.5 (± 0.1), -1.1 (± 0.1), and -1.5 (± 0.2), respectively, all significantly less than zero ($p < 0.001$). Exercise capacity declined significantly over time irrespective of primary diagnosis. We did not find significant determinants of exercise capacity.

Conclusion

Neonates treated with ECMO 5 years later have a significantly worse exercise capacity than expected from recent reference data. Exercise capacity may even further deteriorate, as they grow older. This deterioration was independent of primary diagnosis.

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is a pulmonary bypass technique providing life support in acute reversible cardiorespiratory failure when conventional management fails. It was originally suggested to avoid further lung injury from high oxygen concentration, volutrauma and barotrauma, and hence promotes lung healing. In neonates it was first used over 30 years ago, mainly in congenital diaphragmatic hernia (CDH), meconium aspiration syndrome (MAS), persistent pulmonary hypertension of the newborn, or sepsis. A large trial in the UK conferred a survival advantage of neonatal ECMO over conventional management without a concomitant increase in severe disability.[1-3] Thus, ECMO may be of benefit to infants with severe respiratory dysfunction who otherwise would have died. Detailed assessment of longer-term morbidity is considered essential to substantiate the reported survival advantage.[4]

Neonates treated with ECMO may suffer long-term physical and developmental morbidity. Severity of illness preceding ECMO, severe respiratory failure prior to ECMO, and several factors during ECMO increase the risk of pulmonary dysfunction and cerebral damage.[2,5-8] However, little is known about the effects of ECMO on exercise capacity. Boykin and colleagues reported that the exercise tolerance of 10 - 15 year old children treated with ECMO as neonates for MAS was similar to that of age-matched controls.[5] On the other hand, Hamutcu and colleagues found that 48 children with a mean age of 11 years, treated with ECMO for various underlying diagnoses had lower oxygen saturation with exercise and lower peak oxygen consumption than controls.[9] The time course of these changes remains unclear, and to our knowledge no longitudinal data of exercise tolerance after neonatal ECMO are available.

The aim of the present study was therefore to evaluate whether children treated with ECMO at neonatal age have normal exercise capacity at the long term; how exercise capacity changes over time in these patients, and whether exercise capacity bears a relation to the primary diagnosis.

METHODS

Patients

A longitudinal follow-up study was conducted in children who all received veno-arterial (VA) ECMO support as neonates between January 1992 and August 2004 at the Intensive Care Unit of the Erasmus MC - Sophia Children's Hospital. The cohort was supplemented with 5 children who received VA ECMO in two other ECMO centers (Nijmegen, The Netherlands: n = 4 and Leuven, Belgium: n = 1). The latter both used the same inclusion criteria and treatment protocols as our center. ECMO support was given in case of reversible severe respiratory failure and an estimated mortality risk of higher

than 80% using the entry criteria reported by Stolar et al.[10] Entry criteria and exclusion criteria were previously described by our group[11] and did not change during the study period. The study was part of a structured prospective post-ECMO follow-up program initiated in 2001 that provides for regular assessments of lung function, growth and developmental parameters until 18 years of age.[6,7] Based on the national consensus on neonatal follow-up and the Dutch Ministry of Health's requirement to provide relevant data, the assessment protocol is the standard of care in the Netherlands following ECMO. As a consequence IRB approval was waived. Parents of all children were routinely informed about the study.

Procedures and study design

The following clinical characteristics were recorded prospectively: underlying diagnosis, gestational age, birth weight, age at onset of ECMO, duration of ECMO support, mean airway pressure (MAP) and highest oxygenation index (OI) prior to ECMO, duration of mechanical ventilation before start ECMO, total duration of mechanical ventilation (including ECMO), duration of oxygen dependency and the prevalence of chronic lung disease (CLD). According to the definition of Jobe and Bancalari, CLD was defined as oxygen dependency at day 28. It was classified as mild, moderate or severe, based on the amount of oxygen needed at day 56 or at discharge, whichever comes first.[12]

The assessment protocol encompassed hospital visits at 5, 8 and 12 years. Medical assessment consisted of medical history taking, measurements of growth parameters, and a standardized physical examination. Spirometry and an exercise test were performed when the child was clinically stable. Prior to the exercise test parents estimated their child's fitness level as higher than, equal to or less than that for children of the same age.

Spirometry and exercise tests

Spirometry was performed with a dry rolling seal spirometer (Jaeger, Hoechberg, Germany) according to European Respiratory Society (ERS) criteria.[13] Three forced vital capacity (FVC) manoeuvers were performed and the best values of forced expiratory volume in 1 s (FEV_1) and FVC were recorded.

The children performed a graded, maximum exercise test using a motor-driven treadmill (En Mill, Enraf Nonius, Rotterdam, the Netherlands) programmed for increases in angle of inclination and speed according to the Bruce protocol.[14,15] The maximal endurance time (in minutes, one decimal) served as criterion of exercise capacity. Before and during the test we monitored heart rate and transcutaneous oxygen saturation with a pulse Oximeter (MARS, motion artifact reduction system, type 2001, Respironics Novametrix, Murrysville PA). Heart rate of ≥ 185 beats per min (bpm)[16] or loss of coordination because of over-fatigue was taken as maximal performance.

Data analysis

The OI was calculated as: [(Mean airway pressure x FiO_2)/PaO_2] x 100.[10] The Dutch Growth Analyser, version 3.0 (Dutch Growth Foundation, Rotterdam) served to calculate SDS for height, weight and BMI, on the basis of Dutch reference values published in 2000.[17] Adapted reference values were used for children of Moroccan or Turkish origin.[18,19] SDS-scores for spirometric data were calculated as the difference between observed and predicted value divided by the residual standard deviation from the reference values of Stanojevic et al.[20] The SDS-scores of the maximal endurance time were calculated using recent age-related reference values for healthy Dutch children.[14,15] SDS-scores < -1.96 (2.5^{th} percentile of the reference population) were considered abnormally low. Group comparisons were performed with the Mann-Whitney U test. Longitudinal evaluation of the endurance times at 5, 8 and 12 years was performed using mixed-model ANOVA, which allows for missing data in an optimal way.[21] To investigate whether underlying diagnosis and other determinants have a significant influence on the SDS endurance time we analyzed diagnoses and the following components in the mixed model as covariates: gestational age, birth weight, OI, MAP, time on ECMO, duration of ventilatory support before start ECMO, total duration of ventilatory support, oxygen support after decannulation, the prevalence of CLD, SDS weight at follow-up, SDS height at follow-up, SDS BMI at follow-up, SDS FEV_1, SDS FEV_1/FVC, and sports participation. For continuous parameters with a lognormal distribution (OI, MAP, duration of ventilatory support before start ECMO, total duration of ventilatory support) we transformed the data logarithmically in order to reduce the effect of outlying observations.

Values for two subgroups -CDH and MAS- were analyzed separately. These two subgroups were considered of special interest. CDH is associated with abnormal lung development; infants with MAS form the largest subgroup of children with normal lung development. The other subgroups are small and more heterogeneous with respect to underlying disease. Statistical significance was accepted at a two-sided 5% level for all tests. Statistical analyses were performed using SPSS 15.0 for Windows.

RESULTS

Between January 1992 and August 2004, 240 neonates received ECMO support within 28 days after birth in the Erasmus MC - Sophia Children's Hospital. Sixty-eight of them died before age 5 years (28%). Fifty-nine percent of those children were born with CDH. Five children who received ECMO support elsewhere were included in our follow-up program as well. Thirty-two children were lost to follow-up: refusal to participate (n = 16), not traceable (n = 6), or follow-up elsewhere (n = 10). Their baseline characteristics did not differ from those who were included in the final analysis.

One hundred and forty-five children participated in our follow-up program (82% of all survivors). Fourteen children were not able to perform the exercise test because of neurological problems, such as hemiplegia and seizure disorder (n = 10); chromosomal disorder with mental retardation (n = 2); or behavioural problems (n = 2). These 14 children had been ventilated longer than those who were included in the analysis (Mann-Whitney U test p = 0.027).

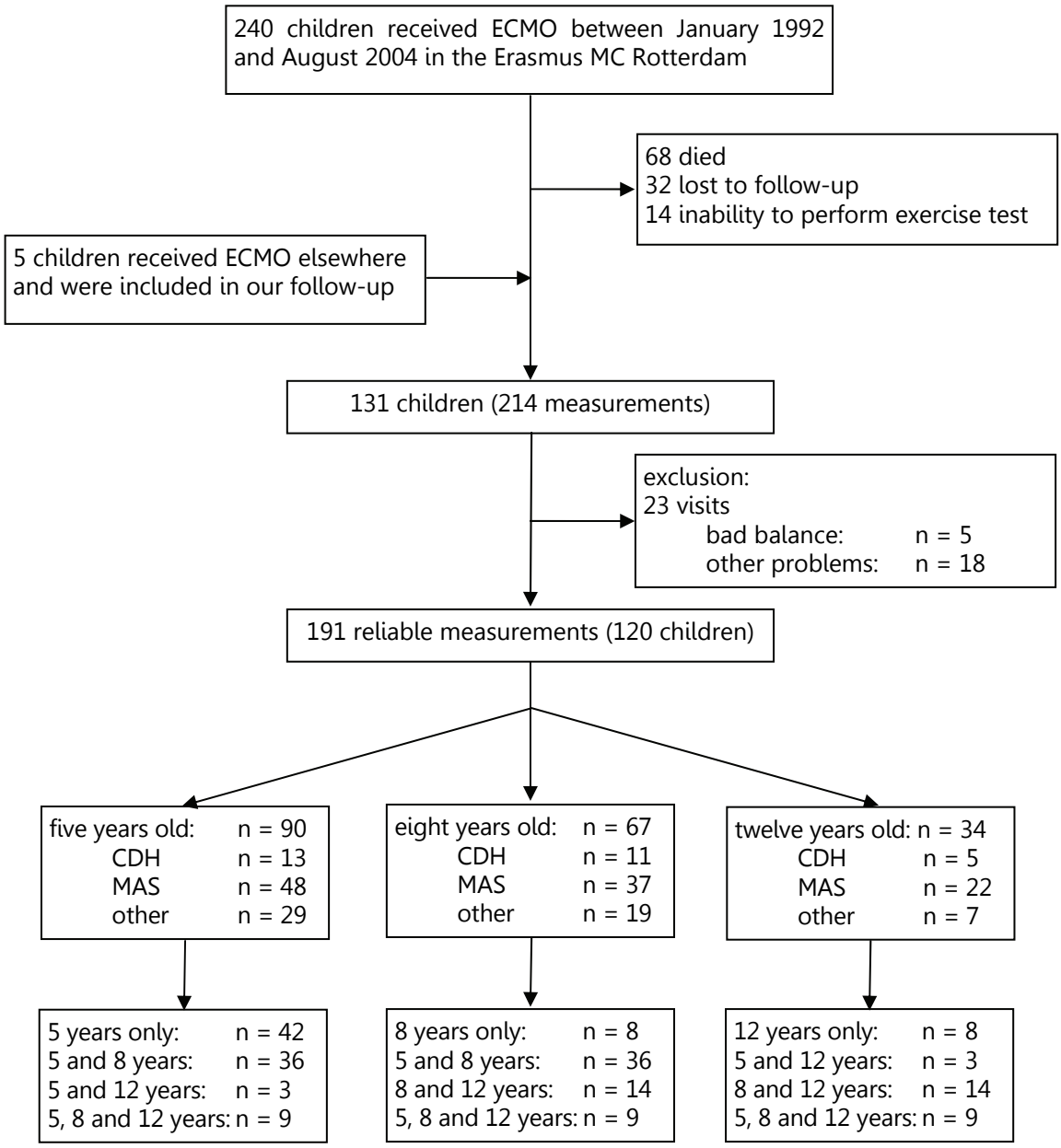

Figure 1 *Flowchart: infants included in follow-up program*

Thus 131 children performed the Bruce treadmill test (214 measurements). We excluded the results of 23 measurements because maximal performance could not be achieved due to balance problems (n = 5) and other reasons such as fear, pain in the legs and

concentration problems (n = 18). The 11 children who did not perform any maximal exercise test had longer oxygen support and more severe CLD than the 120 participants (Mann-Whitney U test p = 0.007 and p = 0.012 respectively). The final analysis concerned 191 exercise tests performed by 120 children (68% of all survivors) (figure 1). The primary diagnoses of these 120 children were: MAS (n = 66), CDH (n = 18), and other diagnoses (n = 36). The diagnoses of the children in the group "other diagnoses" were: persistent pulmonary hypertension of the newborn (n = 20), sepsis (n = 7), pneumonia (n = 6), cardio-respiratory problems (n = 2), congenital cystic adenomatoid malformation of the lung (n = 1). The perinatal characteristics and ECMO treatment characteristics of all survivors are presented in Table 1.

At time of follow-up, the mean SDS FEV_1 was significantly below zero at ages 5, 8 and 12. This also applies to mean SDS FEV_1/FVC at ages 8 and 12. The characteristics at time of follow-up of the children of the study group are presented in Table 2.

Exercise capacity

At ages 5, 8 and 12 years, ANOVA resulted in mean SDS (± SE) endurance time on the Bruce treadmill protocol of - 0.5 (± 0.1), -1.1 (± 0.1) and -1.5 (± 0.2), respectively, all significantly less than 0 (all $p < 0.001$). The SDS was abnormally low (< -1.96) in 6/90 measurements (7%) at age 5, in 10/67 measurements (15%) at age 8, and in 12/34 measurements (35%) at age 12. At the end of the test HR was reliably recorded in 156 measurements (82%) and the 10^{th} and 90^{th} percentiles were 168 and 200 bpm. Technical problems precluded reliable recording of HR in the final stage of the test for the other 35 measurements, but, based on HR in the pre-final stage or loss of coordination, we considered performance in those measurements to be maximal. In five out of 156 measurements there was a decrease in transcutaneous oxygen saturation greater than or equal to 5% from baseline (2 out of 29 measurements in children with CDH and 3 out of 107 measurements in children with MAS). None of the children had transcutaneous oxygen saturation below 90%.

Figure 2 shows the longitudinal evaluation of the SDS endurance time at ages of 5, 8 and 12 years for the total group and for the different initial diagnoses. The mean outcome at age 5 was higher than those at ages 8 and 12 (both $p \leq 0.001$), with a marginal difference between ages 8 and 12: $p = 0.050$. The underlying diagnosis had no significant influence. Further analysis using ANOVA did not show significant relationships with time on ECMO; duration of ventilatory support before start ECMO; total duration of ventilatory support; oxygen support after decannulation; prevalence of CLD; SDS weight at follow-up, SDS height at follow-up; SDS BMI at follow-up SDS FEV_1; SDS FEV_1/FVC; and sports participation (data not shown). The levels of exercise capacity as estimated by the parents were positively correlated with the measured endurance SD scores ($p = 0.002$).

Table 1 *Perinatal and extracorporeal membrane oxygenation (ECMO) characteristics*

	All survivors	**Participants**	**Lost to follow-up**	**Inability to perform exercise test**	**No maximal performance**
	n = 177	n = 120	n = 32	n = 14	n = 11
boys / girls	94 / 83	60 / 60	21 / 11	7 / 7	7 / 4
diagnosis					
MAS, n (%)	96 (54)	66 (55)	17 (53)	6 (42)	6 (55)
CDH, n (%)	29 (17)	18 (15)	3 (9)	4 (29)	4 (36)
other, n (%)	52 (29)	36 (30)	12 (38)	4 (29)	1 (9)
Gestational age, wk	39.7 (1.9)	39.8 (1.8)	39.7 (1.9)	38.7 (2.3)	40.5 (1.5)
Birth weight, kg	3.4 (0.6)	3.4 (0.6)	3.4 (0.6)	3.2 (0.6)	3.7 (0.4)
Oxygenation index	50.8 (22.4)	49.5 (22.0)	56 (24.4)	48 (21.8)	52.9 (23.8)
MAP, (cm. H_2O)	20.0 (4.5)	19.9 (4.4)	20.9 (3.6)	21.7 (5.1)	21.7 (6.9)
Pre-ECMO treatment with NO, n (%)	115 (65)	74 (62)	22 (69)	10 (71)	9 (82)
Age before start ECMO, hours	47.9 (72.8)	48.1 (64.0)	46.1 (59.1)	66.7 (155.4)	21.5 (10.0)
Time on ECMO, hours	147.7 (74.7)	142.5 (65.3)	138.9 (66.0)	211.3 (136.5)	152.7 (56.5)
Ventilatory support, days	16.6 (15.2)	15.2 (12.7)*	15.2 (8.9)	32.1 (34.4)*	17.3 (13.4)
Oxygen support					
one day - one week, n (%)	71 (40)	53 (44)[§]	13 (41)	4 (29)	1 (9)[§]
one week - one month, n (%)	62 (35)	41 (34)	10 (31)	6 (43)	5 (46)
> one month, n (%)	19 (11)	14 (12)	0 (0)	1 (7)	4 (36)
unknown, n (%)	25 (14)	12 (10)	9 (28)	3 (21)	1 (9)
CLD (chronic lung disease)					
none, n (%)	125 (71)	95 (79)[‡]	18 (56)	7 (50)	5 (46)[‡]
mild, n (%)	17 (10)	7 (6)	6 (19)	1 (7)	3 (27)
moderate, n (%)	4 (2)	2 (2)	1 (3)	1 (7)	0 (0)
severe, n (%)	14 (8)	9 (7)	1 (3)	2 (14)	2 (18)
unknown, n (%)	17 (9)	7 (6)	6 (19)	3 (22)	1 (9)

Data shown are mean (SD) or number (%) of patients
* *Mann-Whitney U test, p = 0.027 difference in ventilatory support between children who were unable to perform exercise test and participants*
[§] *Mann-Whitney U test, p = 0.007 difference in oxygen support between children without maximal performance and participants*
[‡] *Mann-Whitney U test, p = 0.012 difference in CLD between children without maximal performance and participants*
MAS = meconium aspiration syndrome; CDH = congenital diaphragmatic hernia; MAP = mean airway pressure; ECMO = extracorporeal membrane oxygenation; NO = nitric oxide

Table 2 *Characteristics at follow-up at ages 5, 8 and 12 years*

	5 years	**8 years**	**12 years**
	n = 90	n = 67	n = 34
boys / girls, n	43 / 47	36 / 31	16 / 18
diagnosis			
CDH, n (%)	13 (15)	11 (16)	5 (15)
MAS, n (%)	48 (53)	37 (55)	22 (65)
other, n (%)	29 (32)	19 (29)	7 (20)
SDS Height	-0.22 (1.28)	-0.15 (1.08)	0.04 (1.13)
SDS Weight	-0.28 (1.55)	0.00 (1.37)	0.05 (1.15)
SDS BMI	-0.19 (1.26)	0.14 (1.24)	0.10 (1.07)
sports participation			
yes, n (%)	54 (60)	54 (81)	25 (74)
no, n (%)	35 (39)	13 (19)	9 (26)
missing, n (%)	1 (1)	0 (0)	0 (0)
parental estimation of fitness level			
better than peers, n (%)	5 (6)	4 (6)	2 (6)
similar to peers, n (%)	63 (70)	47 (70)	22 (65)
worse than peers, n (%)	19 (21)	16 (24)	10 (29)
missing, n (%)	3 (3)	0 (0)	0 (0)
physical therapy at home			
yes, n (%)	6 (7)	3 (5)	0 (0)
no, n (%)	84 (93)	64 (95)	34 (100)
	n = 62	n = 53	n = 28
SDS FEV_1	-0.54 (1.11)*	-0.64 (1.29)*	-1.11 (1.54)*
SDS FEV_1/FVC	-0.11 (1.44)	-0.70 (1.15)*	-1.03 (1.22)*

Data shown are mean (SD) or number (%) of patients
** one sample t-test: mean value significantly different from zero: $p \leq 0.001$*
CDH = congenital diaphragmatic hernia; MAS = meconium aspiration syndrome; SDS = standard deviation score; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity

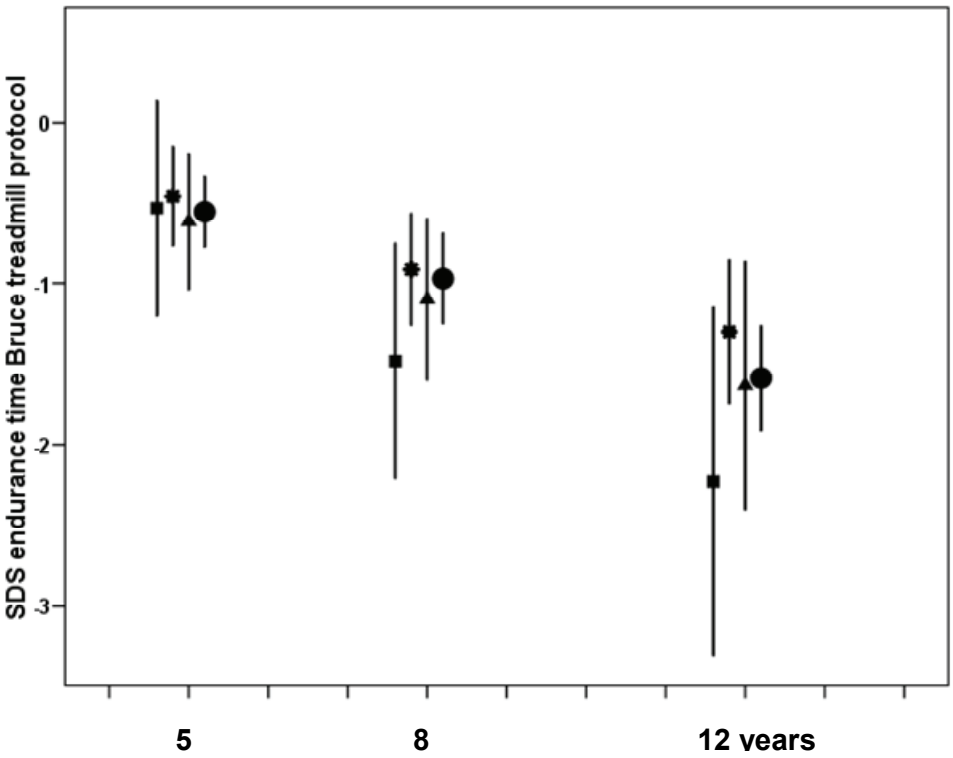

Figure 2 *Exercise capacity at the different ages*
Data shown are ANOVA estimates of mean values with 95% confidence intervals squares: CDH; asterisks: MAS; triangles: remaining group; circles: total group

DISCUSSION

We evaluated exercise capacity at ages 5, 8 and 12 years after neonatal ECMO treatment. Exercise capacity declined significantly over time irrespective of the underlying primary diagnosis. The children's levels of exercise capacity estimated by the parents positively correlated with the endurance SD scores. None of the clinical characteristics correlated with exercise tolerance.

Boykin and colleagues tested exercise capacity in 10 - 15 year old children who as neonates had received ECMO treatment for MAS.[5] The cross-sectional study revealed that the 17 ECMO-treated children had similar aerobic capacity as the age-matched healthy controls. Duration of oxygen use following decannulation proved the most significant factor in predicting long-term pulmonary outcome. In our study the mixed linear model analysis revealed deterioration of exercise capacity irrespective of the underlying diagnosis. Our study population assumedly included more children with initial pulmonary hypoplasia and residual pulmonary sequelae than in the study of Boykin, who only studied MAS patients who have intrinsically normal lungs.

Hamutcu and colleagues studied 48 children with a mean age of 11.1 years, treated with ECMO for various conditions, including MAS and CDH.[9] These children had lower peak

oxygen consumption than healthy age-matched controls. The protocol to determine exercise capacity differed from that used in our study, which hampers comparison of the results. Interestingly, almost 25% of the ECMO-treated children but none of the controls showed oxygen desaturation (SPO_2 < 90%) during exercise. This phenomenon was not observed in any of our participants. Amongst the outcome parameters in the study of Hamutcu and colleagues was the peak oxygen consumption, VO_2max. We did not measure gas exchange parameters for various reasons. Firstly, wearing a mask may lead to loss of cooperation and to sub maximal results, especially in the younger children. Secondly, Cumming et al[22] reported a strong correlation between maximal endurance time and maximal oxygen uptake. They concluded that maximal endurance time might be used as a sole criterion of exercise capacity.

Recently, Gischler and co-workers from our group evaluated maximal exercise performance in 16 five-year-old children born with CDH of whom nine had undergone neonatal ECMO treatment. The mean SDS endurance time was -0.84 (also significantly different from zero: p = 0.012).[23] Peetsold and colleagues evaluated exercise capacity in 53 other survivors of CDH who had not received ECMO treatment.[24] Their mean (SD) age was 11.9 (3.5) years and 36 of them reliable performed the Bruce treadmill test. In most of them the exercise capacity agreed with the reference values of Binkhorst et al established in 1987.[25] There was a positive but small correlation between the SDS VO_2Max and the SDS FEV_1 (R^2 = 0.27; p = 0.001). In our study the correlation between maximal endurance time and SDS FEV_1 was not significant. ECMO offers survival to those children with CDH with more severe lung hypoplasia. The children in the study of Peetsold and colleagues who did not need ECMO at all, represent survivors with a milder form of CDH.

Vrijlandt and colleagues reported on exercise capacity in young adults born prematurely and age-matched controls.[26] As bronchopulmonary dysplasia was over-represented in their prematurely born group, participants with and without bronchopulmonary dysplasia were compared. There was no significant difference in exercise capacity between these subgroups.

Earlier we found balance skills problems in five-year-old children treated with neonatal ECMO.[7] These problems perhaps could (partly) explain the decline in exercise capacity between ages 5 and 8. In the present study, five-year-old children were allowed to hold the guardrail to maintain body position near the centre of the moving belt, unlike older children.[14,15] Hence part of the deterioration between ages 5 and 8 could be explained by possible balance problems. On the other hand, this cannot explain deterioration between ages 8 and 12.

Another possible limitation of our study is the lack of healthy controls. We do not think that this invalidates our findings, as the main purpose of our study was to perform a prospective longitudinal evaluation of exercise capacity. We used reference data for the Bruce treadmill protocol we recently obtained in healthy Dutch children.[14,15] Furthermore, testing at the different ages was done with exactly the same protocol and equipment as in that study and for the most part even by the same investigator.

In conclusion, neonates treated with ECMO are at risk for decreased exercise capacity at school age. We therefore propose prolonged follow-up. Pro-active advice on sports participation or referral to a physical therapist should be considered, especially when parents or children report impaired exercise capacity themselves.

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General discussion and recommendations

INTRODUCTION

Over the last decades, mortality rates in children receiving intensive care have dropped by improved treatment modalities like high frequency oscillation (HFO), inhaled nitric oxide (NO), and -in selected patient groups- extracorporeal membrane oxygenation (ECMO). Better survival coincides, however, with more morbidity, not only because of the underlying disease, but also due to adverse side effects of the intensity of treatment, such as high inspiratory oxygen fraction, shear forces and elevated peak inspiratory pressures during mechanical ventilation. In this thesis we have focused on long-term morbidity in children with congenital diaphragmatic hernia (CDH) or esophageal atresia (EA); two major pediatric surgical diagnosis with concomitant abnormal lung development.

Several cross-sectional studies revealed a wide range of long-term complications in young and adolescent CDH survivors, such as pulmonary problems,[1-3] cognitive, emotional and behavioral problems,[4] chest wall deformities,[2,5] gastro-oesophageal reflux[6] and motor function problems.[7,8] Therefore the American Academy of Pediatrics (AAP) recommended multidisciplinary follow-up after correction of CDH, especially when the defect was large, patch repair was performed or ECMO was applied.[9]

Usui et al observed anatomical anomalies of the tracheobronchial tree in patients with esophageal atresia.[10] And Rintala et al,[11] Sistonen et al[12] and Peetsold et al[13] reported on long-term follow-up after repair of esophageal atresia. Rintala and Sistonen et al showed extended restrictive ventilatory defect into adulthood. Thoracotomy-induced rib fusions and gastro-esophageal reflux-associated esophageal epithelial metaplasia were the strongest risk factors for these ventilatory sequelae. Peetsold et al[13] demonstrated that 6 to 18 years after repair of esophageal atresia, general health remains impaired in comparison with a healthy reference population, mainly because of concomitant anomalies and gastro-intestinal symptoms.

In January 1999 we started a multidisciplinary follow-up program aimed to evaluate and potentially reduce the overall morbidity associated with major anatomical anomalies, to offer better care and to improve lines of communication. In 2001 children treated with ECMO became a target group as well.[14] The pediatric physical therapist in the team evaluates motor development and exercise capacity. From the age of 5 years onwards, motor development is measured with the Movement Assessment Battery for Children (MABC)[15,16] and exercise capacity with the Bruce treadmill protocol[17] or cycle ergometry. The latter is used for children older than 12 years. The Bruce treadmill protocol is a graded maximum exercise test using a motor-driven treadmill with standardized increases in angle of inclination and speed.[17] Dutch reference values were established in 1987. We doubted whether these values reflect contemporary exercise capacity of

healthy Dutch children and hypothesized that exercise capacity has deteriorated over the last decades. Besides, that study included not so many very young children. So, an update of reference values for the Bruce treadmill protocol was felt necessary.

The most important aims of the studies presented in this thesis were:
- to determine new reference values for exercise capacity as indicated with the Bruce treadmill protocol for healthy Dutch children aged 4 - 13 years (Chapters 1 and 2);
- to compare the endurance times on the original and half Bruce protocol in 4- and 5-year-old children (Chapter 2);
- to compare long-term respiratory morbidity in children after repair of EA or CDH (Chapter 3);
- to study motor function and exercise capacity in 5-year-old children born with major anatomical congenital anomalies (Chapter 4);
- to assess exercise capacity, severity of fatigue, and daily activity in young adults with CDH and in matched controls, who underwent similar neonatal treatment (Chapter 5);
- to evaluate the characteristics of motor performance at five years of age in a nationwide Dutch ECMO population (Chapter 6);
- to study exercise capacity in the first 12 years of life after neonatal ECMO (Chapter 7).

This chapter discusses the relevance as well as the limitations of the present studies and the way in which the results could be interpreted. In addition, recommendations for future research are given.

Reference values Bruce treadmill protocol

The Bruce treadmill protocol is well suited for children from the age of 4 years[17] and is preferred to cycle ergometry for clinical exercise testing in children in the United States.[18] In the Netherlands, the Bruce treadmill protocol is used not only in clinical settings but also by local pediatric physical therapists. We established new reference values for the Bruce treadmill protocol in healthy Dutch children aged 4 - 13 years (Chapters 1 and 2 of this thesis). Children aged 6 - 13 years performed the exercise test as prescribed, i.e. without holding the guardrail, but the younger children were permitted to hold the guardrail. We refrained from using a harness because in the Bruce protocol the belt speed is slow and using a harness may lead to loss of cooperation and to submaximal results. In our experience, walking on the treadmill with increments of speed and inclination till maximal performance without rail holding is too difficult for many children aged 4 or 5 years. This is why we, in accordance with daily practice, preferred the safety of holding the rail in these young children. Our strategy enabled more young children to perform this maximal exercise test.

Furthermore, we compared these young children's endurance times on the Bruce protocol with those on the so-called 'half-Bruce' protocol. We also looked at body mass

index (BMI), socioeconomic status (SES), ethnicity, sports participation, and school transport habits as possible determinants of exercise capacity.

In accordance with our hypothesis, the maximal endurance times were indeed lower than those published in 1987.[19] This only held true, however, for children up to the age of 10; the older children performed as well as those in 1987.

Indications for deterioration of exercise capacity were also observed in urban American children and in Danish children. Chatrath and colleagues[20] examined children of 4 to 18 years of age and compared findings with reference values of Cumming et al.[21] Exercise endurance times in this healthy (apart from innocent cardiac murmurs) study population had dropped for all ages. BMI was strongly related with endurance time ($p < 0.0001$). Wedderkopp et al[22] analysed secular trends through two cross-sectional studies performed 12 years apart in 9-year-old children in Odense, a large city in Denmark. Boys in 1997 - 1998 were less fit than those in 1985 - 1986 and in addition they were fatter. Increased polarization is clear from the fact that in 1997 - 1998 the difference between the fit and the unfit as well as the difference between the lean and the fat were greater than in 1985 - 1986. A similar polarization was found in girls, but overall the girls' fitness or obesity had not changed.

In our study, BMI and intense sports participation were most predictive for maximal endurance time in the age group 6 - 13 years. For the younger children there were no significant relations between endurance and the pre-formulated determinants. Intensity of sports participation correlated positively with age. In the Netherlands, children up to 7 years of age spend more time watching television than 5 years earlier and 2% of all children aged 3 years and over never play outdoors.[23] More and more children in the United Kingdom and Australia are being taken to school by car[24,25] and we assume that this holds true for the Netherlands as well. On the other hand, Metcalf found that the school run does not affect overall physical activity of 5-year-olds. The fact that the over-10-year-old's exercise capacity was conform the 1987 values is probably due to increasing sports participation during the past years and stabilization of time spent watching television.[23,26]

Children included in the studies of Chatrath and Wedderkopp were all living in urban regions. To control for living situation we, however, recruited children from both urban and suburban regions. Our sample was representative of the Dutch population with respect to ethnicity. With respect to SES, some selection bias cannot be ruled out. A relatively large proportion of the sample was classified as high SES. The low but significant correlation between SES and SDS endurance we found makes it likely that children with lower SES perform slightly worse. The overall outcome of the study may therefore be slightly overestimated.

The Bruce treadmill protocol has rather large increments in workload between stages. For this reason some pediatric physical therapists in the Netherlands use the so-called 'half-Bruce' protocol for young children. Reference values for the original protocol are then applied. We found differences in endurance time between the two protocols in advantage of the original Bruce protocol and concluded that the original protocol should be preferred also in young children. Our newly established reference values are now being used in our tertiary university hospital, and in other hospitals and local physical therapy practices in the Netherlands as well.

Exercise capacity and motor function in children and young adults born with major anatomical congenital anomalies

In Chapter 3 we describe persistent respiratory morbidity five years after repair of EA and CDH. The children's endurance times on the Bruce treadmill test were lower than reference values. In a study in a larger group with a wider range of anatomical anomalies (Chapter 4) we analyzed motor function as well, using the MABC. Children with small intestinal anomalies and abdominal wall defects showed normal exercise capacity and motor function. Children with EA or CDH had -as described in Chapter 3- impaired exercise capacity but also impaired motor function. Both groups experienced difficulties in gross motor skills, with normal fine motor skills. The score on the MABC correlated positively with maximal endurance time. No significant correlation was found between the MABC score and growth parameters. We interpreted therefore that CDH and EA patients, who suffer from persistent respiratory and gastrointestinal problems during the first years of life, get little physical activity and have fewer opportunities to practice gross motor skills. For that matter, parents may be (over)protective and restrain the child in physical activity for fear of respiratory distress. Holm and Bjarnason[27,28] reported a similar parental protection in children with cardiac malformations. Most children with small intestinal anomalies or abdominal wall defects have few problems beyond the first few months of life[29] and may have more opportunities for physical activity and hence for improving motor competence. A limitation of our studies is that the number of subjects per subgroup was small, thus precluding firm conclusions.

We also evaluated cardiopulmonary function of young adults who as newborns had been operated on for CDH. Findings were compared with those in term born age-matched controls without CDH or lung hypoplasia who as newborns had received similar intensive care treatment. Testing was performed on an electrically braked cycle ergometer. We used reference values of Shvartz and Reynolds.[30] VO_2peak values in CDH patients and in age-matched controls were lower than reference values. However, there were no obvious differences in test values between both groups. It would seem, therefore, that not only residual consequences of CDH (like pulmonary hypoplasia) but also neonatal respiratory insufficiency and intensive care treatment affect cardiopulmonary function.

Because of changes in neonatal management of CDH with preoperative stabilisation, and the use of HFO, NO and ECMO nowadays, patients with more severe lung hypoplasia have the opportunity to survive. It is therefore conceivable, that our group of patients is -in general- less affected than patients born nowadays. Also, new treatment modalities in itself may possibly result in new complications, like intracranial injuries[31] or prolonged use of opioids and/or benzodiazepines with an unknown long term effect.[32] On the other hand, ECMO may ameliorate the harmful effects of mechanical ventilation or somehow preserve lung-function in the very ill neonate.[33]

A limitation of this study is the lack of recent reference values for exercise capacity in young adults, indicated as VO_2peak. We felt that the reference values of Shvartz are most appropriate for our study population. To strengthen our conclusions we recalculated our results with reference values of Wasserman et al,[34,35] Jones et al[36] and Fairbarn et al[37] Only in comparison with values of Wasserman et al the groups scored within the normal range and -in agreement with our conclusion- none of the recalculations yielded a significant difference between the groups (see Table).

Table *Results Cardiopulmonary Exercise Testing*

	CDH	**Control patients**	**Paired samples test**
VO_2peak	n = 26	n = 27	
% Pred Shvartz ml/min/kg[30]	84.0 (16.1)[†]	84.7 (14.4)[†]	p = 0.95
% Pred Wasserman[34,35]	96.5 (15.4)	98.0 (14.1)	p = 0.78
% Pred Jones[36]	91.6 (16.8)[§]	89.3 (13.7)[†]	p = 0.47
% Pred Fairbarn[37]	75.3 (14.0)[†]	78.5 (11.6)[†]	p = 0.53

[†] *One sample t-test p < 0.001 (patients versus norm scores)*
[§] *One sample t-test p = 0.017 (patients versus norm scores)*

Recently, Vrijlandt et al compared exercise capacity of 41 pre-term born Dutch young adults with that of 47 healthy controls.[38] On the basis of the reference values of Wasserman et al, the ex-preterms had a lower exercise level and VO_2max than the healthy controls.[35] The healthy controls mean VO_2max of % predicted was higher than 100%, however, so we may assume that values of Wasserman et al slightly underestimate exercise capacity of present-day healthy Dutch young adults.

Another possible limitation is the fact that no cardiac evaluation was performed. Hayward et al[3] showed that many CDH patients develop significant and progressive ventilation/perfusion mismatches.

Besides exercise capacity we studied severity of fatigue in both groups. We found no significant differences between the groups, but were somewhat alarmed that 37% of the

CDH patients reported a certain degree of fatigue. In addition, we measured level of daily activity with an accelerometry-based activity monitor during 48 hours in 15 CDH survivors and 13 controls and compared findings with those of 45 healthy subjects recruited from a database of the Department of Rehabilitation Medicine of our institution. The CDH survivors and the controls proved to be as active as healthy young Dutch adults. Testing was, as much as possible, applied in the home situation to avoid interference with the normal activity pattern. Participants were instructed to continue their ordinary life; however, they were not allowed to swim or take a bath or shower. Validity of this measurement may be threatened by participant reactivity, the mechanism whereby persons adapt their normal behaviour because they are being studied. Reactivity can be attributed not only to awareness, but also to experiencing burden from the instrument. However, because reactivity may occur in both patients and healthy persons, we do not expect this to have interfered with the main findings of our study. Furthermore, a recent study on reactivity in patients with spinal cord injury suggests that wearing this particular monitor does not systematically influence the amount of daily physical activity.[39] Interpretation of the results: young adult survivors of CDH and their controls both showed to have diminished maximal exercise capacity. In daily life, however, the CDH survivors and the controls proved to be as active as healthy young Dutch adults. Thirty-seven percent of the CDH patients reported fatigue. So, with a similar activity level as healthy controls during the day, fatigue was clearly present in the daily life of quite a few CDH survivors.

Motor function and exercise capacity after neonatal ECMO

In 2006 we reported on overall morbidity in Dutch ECMO survivors at the age of five years.[40] The present studies aimed to evaluate in more detail motor performance in 5-year-old ECMO survivors and development of exercise capacity from ages 5 to 12 years. Meconium aspiration syndrome, CDH, sepsis and persistent pulmonary hypertension of the newborn (PPHN) are the major indications for ECMO in neonates. The Erasmus MC-Sophia Children's Hospital Rotterdam and the Radboud University Medical Center Nijmegen are the two designated ECMO centers in the Netherlands. In 5-year-old ECMO survivors from both centers we studied motor performance and relations between motor performance problems, health status, cognitive and behavioral problems (Chapter 6). Motor problems in the 140 tested children proved more prevalent than expected on the basis of reference values.[15,16] Thirty-two per cent of the children (vs 15% expected) had mild or moderate motor problems. Problems in gross-motor skills contributed most to this outcome and morbidity was highest in the CDH group.

Evaluating exercise capacity in survivors of neonatal ECMO we found significantly lower endurance times on the Bruce treadmill test at ages 5, 8 and 12 years than expected on the basis of reference values. The mean SDS endurance time at age 5 was higher than those at ages 8 and 12 (both $p \leq 0.001$), with a marginal difference between ages 8 and

12 (p = 0.050), implying that ECMO survivors' exercise capacity deteriorates over time. In this study the underlying diagnosis had no significant influence. We expected that CDH would have shown the worst outcome. We can only speculate that sample numbers were too small to detect significant differences.

Earlier we found balance skills problems in 5-year-old ECMO survivors.[41] In the present study, the five-year-olds were allowed to hold the guardrail, unlike older children.[42,43] Hence part of the deterioration between ages 5 and 8 could be explained by possible balance problems. On the other hand, this cannot explain deterioration between ages 8 and 12. A limitation of the study was the single-center design. We had to resort to the single-center design because the Nijmegen center lacked data of 12-year-olds and also because testing differed between centers. On the other hand, this gave us the opportunity to use the same protocol and equipment as in the reference studies (Chapters 1 and 2 of this thesis). Besides, testing could now be supervised for the most part by one and the same investigator, which -in our opinion- adds credibility to the conclusion. The findings from this study point out the relevance of long-term evaluating of exercise capacity in ECMO treated patients.

Main Conclusions

Reference values Bruce treadmill protocol

Our hypothesis that exercise capacity might have deteriorated over the years was confirmed for healthy Dutch children aged 6 - 10 years. In healthy Dutch children between the ages of 11 and 13 exercise capacity does not seem to have changed. Intensive sports participation and BMI correlate with endurance time in 6 - 13 year old healthy children. Four- and 5-year-olds are capable of performing the original Bruce protocol when holding the rail. This strategy enabled more young children to perform this maximal exercise test.

Exercise capacity and motor function in children and young adults born with major anatomical congenital anomalies

Children born with esophageal atresia or CDH are at risk for long-term respiratory morbidity, disturbed maximal exercise performance, delayed motor (especially gross motor) function performance, and growth impairment. We found a positive correlation between motor function and exercise capacity. Both young adult CDH patients and controls -with similar neonatal intensive care treatment- have reduced exercise capacity. We found few differences between these groups, indicating that not only residual sequelae of CDH but also neonatal respiratory insufficiency and intensive care treatment contributed to the outcome of CDH in adulthood. Patients from the CDH group have more difficulties in daily activities and social participation as reported on the LIFE-H

questionnaire than participants in the group of age-matched controls. Severity of fatigue correlated negatively with exercise capacity.

Motor function and exercise capacity after neonatal ECMO

Neonatal ECMO may carry the risk of developmental problems, most prominently in the motor domain; CDH brings more risk than meconium aspiration syndrome (MAS). There is a risk of lower exercise capacity at school age as well; and exercise capacity even declines over time irrespective of the underlying primary diagnosis.

RECOMMENDATIONS FOR CLINICAL PRACTICE

We recommend using the original Bruce protocol - rather than the half protocol - in children of 4 - 13 years old. Children aged 4 and 5 years are herewith allowed to hold the guardrail so maximal performance can be achieved. In this case it is important to emphasize that rail holding only implies touching the rail to maintain body position near the center of the moving belt, without support of body weight. Older children should hold the rail no longer than 5 seconds during changes of speed and angle of inclination. We also recommend using our newly established reference values for maximal exercise testing with the Bruce treadmill protocol in 4 - 13 year-old children in the Netherlands and probably in other countries in Western Europe as well. Furthermore it is important to confirm validity of the new established reference values within the foreseeable future, because of increasing obesity.

For children with CDH or esophageal atresia, especially those who suffered from a complicated course, we recommend standardized multidisciplinary follow-up until adulthood, with assessment by a pediatric physical therapist from an early age onwards. For our own follow-up program this implicates a standard assessment by a pediatric physical therapist from the age of 24 months onwards. Indications of impaired or delayed motor development or fatigue are reasons for earlier referral to the pediatric physical therapist. Children with uncomplicated other malformations need to be referred to a pediatric physical therapist only on indication. Furthermore, parents of children with CDH or esophageal atresia and of children treated with ECMO, should be stimulated to provide an active life style for their children, with sports activities from a young age onwards.

In CDH cardiac evaluation aimed at assessing the presence of persistent pulmonary hypertension is recommended.

In general we recommend creating better opportunities for children to be physically active in their daily environments (e.g. schools, roads, sports). Importantly, safe places in their own neighbourhood should be available for sports activities. Sports

accommodations should be accessible to children from low-income families as well. Furthermore we recommend to re-introduce school swimming lessons and gymnastic lessons given by qualified instructors and to aim at better eating habits, for instance by paying attention to healthy daily diets and school lunches and by educating parents.

RECOMMENDATIONS FOR FUTURE RESEARCH

In the light of our findings, we recommend to investigate whether early intervention programs would contribute to better motor function and exercise capacity. We assume that modern-day technologies such as active computer gaming, interactive monitoring and advanced pedometers may stimulate children to be physically active and could therefore be of interest in this aspect. It would be valuable to develop an instrument to quantify children's daily activities. Furthermore we believe that a questionnaire like "The Child Vulnerability Scale"[44] could be of great interest to understand underlying phenomenon's in (over)protection by the parents of children with respiratory problems after birth.

Multi-center studies with larger numbers of patients, standardized care and data mining are important to determine risk factors for delayed motor performance and exercise capacity.

It is important to gather longitudinal data of exercise capacity in healthy Dutch children and in children with congenital anomalies as well. We shall then be able to compare each individual patient with healthy peers and with patients with the same anomaly.

Maximal exercise capacity of the over 11 year olds is usually tested using bicycle ergometry. Treadmill testing is recommended for younger children because they have relatively undeveloped knee extensors.[45] Peripheral muscle fatigue has been proven to limit exercise tolerance in adults with chronic obstructive pulmonary disease.[46] We don't know if peripheral muscle fatigue plays a role in our population as well. Extending our follow-up until the age of 18 years means that we have to investigate whether treadmill or bicycle ergometry represents real maximal exercise capacity in the 12 - 18 years old. It is therefore that we recommend to test groups of 12- and 18 year-old CDH and esophageal patients with both the Bruce treadmill protocol and bicycle ergometry. Monitoring VO_2peak during both exercise test modalities could be of great help in identifying the best method for prolonged exercise testing until adulthood.

The selection of normal values for use in the interpretation of cardiopulmonary exercise testing is critical to any interpretative scheme. At this moment several sets of reference

values are available for interpretation of VO_2max. Establishing one single standard is necessary to facilitate interpretation and optimize clinical application.[34]

MAJOR FINDINGS AND RECOMMENDATIONS

The studies presented in this thesis show that children with anatomical congenital anomalies such as esophageal atresia or congenital diaphragmatic hernia, and those treated with ECMO, are at risk for long-term pulmonary morbidity and negative effects on exercise capacity and motor function development.

Intensive follow-up with recommendations regarding life-style and sports activities is important. In addition, we recommend further studies to investigate whether early intervention programs contribute to better motor function and exercise capacity.

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Summary
&
Samenvatting

SUMMARY

Part I Reference Values Bruce Protocol

In **Chapter 1** we present an update of children's reference values for the Bruce treadmill protocol. An update was felt necessary as the values used so far date back to 1987 and children's activity levels were thought to have dropped since. We recruited 267 healthy children aged 6 - 13 years who were willing to perform a treadmill test. They attended five primary and secondary schools in the Southwestern part of the Netherlands, in both urban and suburban regions. Exclusion criteria were: impaired motor development, use of medication affecting exercise capacity, or pulmonary and cardiovascular disease. Furthermore, children who were found to be obese (weight for height ratio above +2 SDS) were excluded from analysis. The maximal endurance time on the treadmill was the criterion of exercise capacity. The children were not permitted to hold on to the guardrail, except briefly to regain balance during changes of speed and angle of inclination. Data were presented for boys and girls separately and we constructed age-related reference centiles. For children up to the age of 10 years the maximal endurance times were indeed lower than the 1987 values. However, the values for the older children had not much changed. Body mass index proved negatively associated with the endurance time, intense sports participation positively (β = -0.412 and 0.789, respectively; $p < 0.001$).

In conclusion, we recommend that these newly established reference data should be the new standard. Furthermore, a better daily environment and a healthy eating pattern could well improve children's exercise capacity.

In **Chapter 2** our primary objective was to determine reference values for healthy children aged 4 and 5 years using the original Bruce protocol. We also compared the endurance times on the original and the half-Bruce protocol and evaluated possible determinants for exercise capacity. In view of their young age the children were permitted to hold the guardrail to maintain body position near the center of the moving belt. The exclusion criteria were similar to those for the older children. Data from 78 children were evaluated. New age-related reference values for boys and girls separately were derived from the maximal endurance times of children who had no former experience with walking on the treadmill. Maximal endurance time seemed to have deteriorated in comparison with values, established in 1987. To answer the question about the difference between the two protocols 53 children were randomly allocated to start with either the original or the half-Bruce protocol. The mean (SD) endurance time using the original protocol was 10.2 min (SD 1.5); that using the half-protocol was 9.4 min (SD 1.3). The mean difference was 50 seconds (95% CI: 29 - 71 s, $p < 0.001$). There were no significant relations between any of the investigated determinants and the maximal endurance times. In conclusion, we recommend implementing our new

established reference data, to use the original Bruce protocol in these young children and to give them the opportunity to hold the guardrail so maximal performance can be achieved.

Part II Congenital Anomalies

In **Chapter 3** we describe a prospective comparative study on growth, persistent gastrointestinal and respiratory morbidity, and exercise capacity in children with esophageal atresia (EA) or congenital diaphragmatic hernia (CDH). Children were seen at 6, 12 and 24 months and at 5 years of age. Respiratory morbidity and physical condition were evaluated at all moments. At age 5 years, pulmonary function and exercise capacity were tested. Children in both the EA and the CDH group showed significantly impaired growth. In the EA group, though, catch-up growth was seen at age 5 years. Extracorporeal membrane oxygenation (ECMO) treatment in CDH patients was a negative predictor for growth. Gastro-esophageal reflux and feeding problems were seen in either group. Bronchopulmonary dysplasia was found in half of the CDH patients (81% in those treated with ECMO); recurrent respiratory tract infections were found mainly in EA patients. Pulmonary function testing revealed abnormally low FEV_1 (% predicted) in 25% of patients in either group.

Both in EA and CDH patients the maximal exercise tolerance was significantly below the norm (mean standard deviation score (SDS) endurance time, -0.60; $p = 0.02$ and -0.84; $p = 0.012$, respectively). Two EA patients (12.5%) showed slightly decreased oxygen saturation (i.e. ≤ 94%) at maximal exercise (94 and 93% respectively). This phenomenon was not observed in any of the CDH patients. We concluded that EA and CDH carry equal risk of long-term respiratory morbidity, growth impairment, and lower exercise capacity.

In **Chapter 4** we investigated a larger group of children with a wider range of anatomical anomalies. One hundred and two children participated in this study that evaluated motor function and exercise capacity in 5 year olds, who were born with CDH, EA, small intestinal anomalies (SIA) or abdominal wall defects (AWD). All 102 children were tested using the Movement Assessment Battery for Children (MABC). Seventy-three children (71.6% vs 85.0% expected) had a total impairment score (TIS) within the normal range, eighteen children (17.6% vs 10.0% expected) were classified as borderline, and another eleven (10.8% vs 5.0% expected) as having a motor problem. This distribution is significantly different from reference values (Chi-square $p = 0.001$). Most problems were encountered with ball skills (Chi-square $p < 0.001$) and balance (Chi-square $p < 0.001$) but not with manual dexterity. TIS of the children with CDH and EA differed significantly from the reference population ($p = 0.001$ and 0.013, respectively). Ball skills were impaired in CDH and EA patients; children with EA also had problems with balance. Maximal exercise performance was analyzed with the Bruce treadmill test. Overall, the children performed worse than the reference population:

mean SDS endurance time = -0.49; p = 0.001, due to poor maximal exercise performance in CDH and EA patients. The percentile score on the MABC correlated negatively with the total number of major congenital anomalies (r_s = -0.27, p = 0.007), and positively with the SDS of the maximal endurance time (r_s = 0.33; p = 0.002). A significant negative correlation was also found with duration of hospitalization and number of surgical interventions (r_s = -0.29; p = 0.003 and r_s = -0.27; p = 0.006). So, we concluded that children with congenital anomalies are at risk for delayed motor function performance and exercise capacity, especially those with CDH and EA and those with additional anomalies associated with longer hospitalizations and multiple surgical interventions.

In **Chapter 5** we determined long-term outcome of exercise capacity, severity of fatigue, and level of physical activity in young adults born with congenital diaphragmatic hernia (CDH). We studied 27 young adults with CDH and 30 age-matched controls without CDH and lung hypoplasia, who underwent similar neonatal intensive care treatment. The control patients had been matched as best as possible for age at follow-up, gestational age, birth weight, duration of artificial ventilation, duration of supplemental oxygen, and sex. Maximal cardiopulmonary exercise testing (CPET) was performed on an electrically braked cycle ergometer. Cardio respiratory fitness was defined as the mean oxygen uptake during the last 30 s of exercise (VO_2peak: in ml/min/kg). Mean VO_2peak (ml/min/kg) in both groups was significantly lower than normal (CDH 84.0% and controls 84.7% predicted (pred); p < 0.001 in both groups compared to normal reference). No significant differences between the groups were found in exercise capacity, degree of fatigue, and level of physical activity. In CDH patients, the score on the Fatigue Severity Scale was negatively related with VO_2peak (ml/min/kg) % pred (R = -0.49; p = 0.01). More CDH patients reported difficulties in their daily activities as estimated with the Life-H questionnaire. We concluded that not only residual sequelae of CDH but also neonatal respiratory insufficiency and intensive care treatment contributed to the outcome of CDH in adulthood.

Part III Follow-up ECMO

In **Chapter 6** we examined motor performance and neuropsychological development in 149 five-year-olds who as neonates had undergone extracorporeal membrane oxygenation (ECMO) treatment. They had been treated between 1993 and 2000 in either of the two designated ECMO centers in the Netherlands (Radboud University Medical Centre Nijmegen and Erasmus MC - Sophia Children's Hospital Rotterdam). Most neonates receiving ECMO suffer from meconium aspiration syndrome (MAS), congenital diaphragmatic hernia (CDH), sepsis or persistent pulmonary hypertension (PPHN). Assessment included an examination by a pediatrician, the Movement Assessment Battery for Children (MABC), the revised Amsterdam Intelligence test (RAKIT) and the Child Behaviour Checklist (CBCL). Almost half of the children showed normal development in all

domains. A one-sample Chi-Square test showed lower MABC total scores ($p < 0.001$) in children with CDH, sepsis and PPHN, but not in children with MAS. Ball skills and balance skills were the most problematic aspects. RAKIT and CBCL scores did not differ from the reference population. Total MABC scores, growth and CBCL were not related to each other, but negative motor outcome was related to lower intelligence quotient (IQ) scores ($r = 0.48$, $p < 0.001$). We concluded that children treated with ECMO as neonates are at high risk for developmental problems, most prominently in the motor domain. Objective evaluation of the long-term morbidity associated with the application of ECMO is best done in an interdisciplinary follow-up program using norm-referenced tests. An international consensus on timing and actual testing protocol should be established.

In **Chapter 7** we assessed exercise capacity in the first 12 years of life after neonatal ECMO, and we evaluated the effect of primary diagnosis, lung function or perinatal characteristics on exercise capacity. Our study concerned 191 exercise tests according to the Bruce treadmill protocol performed by 120 children in the age of 5, 8 and 12 years. We performed three different diagnoses groups: meconium aspiration syndrome ($n = 66$); congenital diaphragmatic hernia ($n = 18$); and other diagnoses ($n = 36$). At ages 5, 8 and 12 years, ANOVA resulted in mean SDS (± SE) endurance time on the Bruce treadmill protocol of -0.5 (± 0.1), -1.1 (± 0.1) and -1.5 (± 0.2), respectively, all significantly less than 0 (all $p < 0.001$). Exercise capacity declined significantly over time irrespective of primary diagnosis. We did not find significant determinants of exercise capacity. We therefore propose prolonged follow-up. The children's levels of exercise capacity, estimated by the parents, correlated positively with the endurance SD scores. Pro-active advise on sports participation or referral to a physical therapist should be considered, especially when parents or children report impaired exercise capacity themselves.

In the last chapter, the **General Discussion** we discuss our findings and make recommendations for future studies.
Our most important recommendations are:

- to investigate whether early intervention programs would contribute to better motor function and exercise capacity in children born with CDH or esophageal atresia
- to initiate multi-center studies with larger numbers of patients. Standardized care and data mining are important to determine risk factors for delayed motor performance and exercise capacity
- to investigate whether treadmill or bicycle ergometry represents real maximal exercise capacity in the 12 - 18 years old CDH and esophageal atresia patients. It is therefore that we recommend testing groups of 12- and 18 year-old CDH and esophageal atresia patients with both the Bruce treadmill protocol and bicycle ergometry.

SAMENVATTING

Door betere behandelingsmogelijkheden op de intensive care voor kinderen zijn de overlevingskansen voor kinderen die geboren worden met ernstige anatomische afwijkingen én voor kinderen die ernstig ziek zijn rond hun geboorte sterk toegenomen. Het aantal kinderen met restafwijkingen neemt hierdoor echter ook toe. Het is belangrijk om deze kinderen binnen een multidisciplinair follow-up team te volgen, enerzijds om vast te leggen hoe het op de lange duur met de kinderen gaat, anderzijds om de eventuele ziektelast zoveel mogelijk te beperken. Binnen dit follow-up team is het de taak van de kinderfysiotherapeut om de motorische ontwikkeling en het duuruithoudingsvermogen van de kinderen in kaart te brengen, om ouders te adviseren en om de kinderen zo nodig door te verwijzen voor therapie.

Deel 1 van dit proefschrift behandelt het verzamelen van nieuwe normwaarden voor het Bruce-protocol, een inspanningstest op de loopband die gebruikt wordt om het duuruithoudingsvermogen van kinderen in kaart te brengen. Het Bruce-protocol is een maximaal test, waarbij snelheid en hellingshoek van de loopband elke 3 minuten volgens een vast protocol oplopen. De tot nu toe gebruikte normwaarden dateren uit 1987 en onze hypothese was dat deze -onder andere door een verminderd activiteiten-patroon bij de huidige generatie kinderen- niet meer voldoen voor kinderen van nu.

In **hoofdstuk 1** wordt het opnieuw normeren van het Bruce-protocol bij kinderen van 6 t/m 13 jaar gepresenteerd. Tweehonderdzevenenzestig gezonde kinderen deden mee aan ons onderzoek. De kinderen werden gerekruteerd op 5 verschillende scholen in het zuidwesten van Nederland. De tijd dat de kinderen de inspanningstest volhielden was de belangrijkste uitkomstmaat van ons onderzoek. Een vertraagde motorische ontwikkeling, hart- en longziekten en het gebruik van medicatie die van invloed zou kunnen zijn op het uithoudingsvermogen, waren redenen dat kinderen uitgesloten werden van deelname aan ons onderzoek. Ernstig overgewicht was een reden om het resultaat niet mee te nemen in de analyse. We presenteerden onze uitkomsten voor jongens en meisjes afzonderlijk. De kinderen tot de leeftijd van 10 jaar leken slechter te presteren dan de kinderen uit de studie van 1987. De uitkomsten van de oudere kinderen kwamen echter goed overeen met de eerdere studie. Kinderen die intensief sportten presteerden het best, terwijl kinderen die relatief zwaar waren voor hun lengte het lopen juist minder lang volhielden.

We adviseren om deze nieuw vastgestelde normwaarden te gebruiken als referentiewaarden bij toekomstig onderzoek. Belangrijk hierbij is dat de kinderen tijdens de test de leuning van de loopband niet mogen vasthouden, behalve gedurende 5 seconden tijdens de veranderingen in snelheid en hellingshoek.

In **hoofdstuk 2** beschrijven wij inspanningstesten op de loopband bij kinderen van 4 en 5 jaar. Het eerste doel van ons onderzoek was om ook voor deze leeftijdcategorie nieuwe normwaarden voor het Bruce-protocol vast te stellen. Bovendien hebben wij de volhoudtijd op het Bruce-protocol vergeleken met die op het zogenaamde "halve" Bruce-protocol en hebben wij gekeken of er voorspellende factoren vastgesteld konden worden voor het duuruithoudingsvermogen van de kinderen. In deze studie was het de kinderen -bij beide inspanningstesten- wel toegestaan om de leuning losjes vast te houden. Het zogenaamde 'halve' Bruce-protocol wordt door verschillende kinderfysiotherapeuten in Nederland gebruikt bij jonge kinderen. De snelheid en hellingshoek van de loopband loopt bij dit protocol in kleinere stapjes op. De exclusiecriteria van de studies bij deze jonge kinderen waren gelijk aan die van de studie bij de oudere kinderen. Achtenzeventig kinderen participeerden in ons onderzoek. Om onze eerste onderzoeksvraag te beantwoorden werden de uitkomsten van kinderen gebruikt die geen eerdere inspanningstest op de loopband hadden uitgevoerd. Er werden wederom normwaarden berekend voor jongens en meisjes afzonderlijk. De volhoudtijd van de kinderen uit deze studie was lager dan die van de kinderen van de eerdere studie (1987). Om te onderzoeken of er een verschil in volhoudtijd is tussen het oorspronkelijke en het halve Bruce-protocol hebben 53 kinderen beide testen uitgevoerd. Er werd door middel van loting bepaald met welk van de twee testen het kind begon. De gemiddelde volhoudtijd bij het originele protocol was 10,2 minuten; dit was 9,4 minuten bij het halve Bruce-protocol. Het gemiddelde verschil was 50 seconden. Er werden geen significante relaties gevonden tussen een van de onderzochte determinanten en de volhoudtijd.

Wij raden naar aanleiding van deze studie aan om kinderen van 4 en 5 jaar te testen met het originele Bruce-protocol en om het kind toe te staan de leuning losjes vast te houden.

Deel 2 van het proefschrift beschrijft de motorische ontwikkeling en het duuruithoudingsvermogen bij kinderen en jongvolwassenen die geboren zijn met ernstige anatomische afwijkingen.

Hoofdstuk 3 beschrijft kinderen met een oesophagusatresie (OA) en kinderen met een congenitale hernia diafragmatica (CHD). Bij kinderen met OA is de slokdarm niet goed aangelegd (onderbroken) en loopt daardoor niet goed door. Kinderen geboren met CHD hebben een aanlegstoornis van het middenrif, waardoor buikorganen in de borstholte liggen en de longen zich minder goed hebben kunnen ontwikkelen. In de studie, beschreven in dit hoofdstuk, hebben we gekeken naar eventuele aanhoudende maagdarm- en luchtwegklachten en naar het duuruithoudingsvermogen. Wij zagen de kinderen terug op onze polikliniek op de leeftijd van 6, 12 en 24 maanden en op de leeftijd van 5 jaar. In beide groepen bleef de groei achter in vergelijking met de

Nederlandse norm. Alleen in de groep kinderen met OA werd aan het eind van de studieperiode een inhaalgroei gezien. Beide groepen vertoonden reflux (het terugstromen van maaginhoud in de slokdarm) en voedingsproblemen; 35% van de kinderen in beide groepen onderging hiervoor een chirurgische ingreep. De helft van de kinderen met CHD had luchtwegklachten in de vorm van bronchopulmonale dysplasie (chronische longaandoening). In de groep die met ECMO werd behandeld was dit zelfs 81%. ECMO is een techniek waarbij het bloed door een hart-longmachine stroomt en daar van zuurstof wordt voorzien. De kinderen met OA hadden vooral last van terugkerende luchtweginfecties. Tracheomalacie (slappe luchtpijp) is een bekend fenomeen bij kinderen met OA, maar de incidentie van andere aanhoudende luchtwegklachten lijkt over het algemeen te worden onderschat. In beide groepen kinderen was het gemiddelde duuruithoudingsvermogen slechter in vergelijk met gezonde leeftijdsgenootjes. Bij 2 kinderen met OA daalde de zuurstofsaturatie tot onder de 95% bij maximale inspanning. Dit fenomeen werd niet gezien bij kinderen met CHD.

Wij concludeerden dat beide patiëntengroepen een verhoogd risico hebben op langdurige luchtwegklachten, groeiachterstand en een lager uithoudingsvermogen. Multidisciplinaire follow-up is daarom voor beide patiëntengroepen van groot belang.

Hoofdstuk 4 gaat in op de motorische ontwikkeling en het duuruithoudingsvermogen van 102 kinderen met verschillende aangeboren afwijkingen (CHD, OA, kinderen met buikwanddefecten en met een aanlegstoornis van de darmen). Wij onderzochten de kinderen op de leeftijd van 5 jaar. De motorische ontwikkeling werd geëvalueerd met behulp van de Movement Assessment Battery for Children (MABC). De MABC test verschillende motorische vaardigheden: handvaardigheden, balvaardigheden en het statisch- en dynamisch evenwicht. Voor bijna driekwart van de kinderen (71,6%) bleven de scores binnen de norm, 17,6% had een verhoogd risico op een motorisch probleem en 10,8% had inderdaad problemen met de motoriek. Deze verdeling is significant verschillend van die in de normpopulatie. De opdrachten die de balvaardigheden testen waren vooral moeilijk voor de kinderen met een CHD en voor kinderen met een OA. De laatstgenoemden vertoonden ook evenwichtsproblemen. Het duuruithoudings-vermogen werd getest met behulp van een inspanningstest op de loopband: het Bruce-protocol. We gebruikten onze recent verzamelde normwaarden als referentie. Over het algemeen genomen scoorden de kinderen met aangeboren afwijkingen slechter dan hun gezonde leeftijdsgenootjes. Nader onderzoek wees uit dat het voornamelijk de kinderen met een CHD en OA waren die onder de norm scoorden. De problemen met de motoriek bleken samen te hangen met het aantal bijkomende afwijkingen, de duur van de ziekenhuisopname en het aantal operaties dat de kinderen in de eerste twee levensjaren hadden ondergaan. Bovendien was er een samenhang tussen de uitslag van de motorische test en de inspanningstest.

Wij adviseren vroegtijdige aandacht voor de motorische ontwikkeling en het duuruithoudingsvermogen, vooral wanneer er sprake is van CHD of OA met bijkomende afwijkingen, langdurige ziekenhuisopname en veelvuldig chirurgisch ingrijpen.

In **hoofdstuk 5** onderzochten wij de langetermijngevolgen op het gebied van duuruithoudingsvermogen, mate van vermoeidheid en van fysieke activiteit bij jongvolwassenen die geboren zijn met CHD. We onderzochten 27 jongvolwassenen met CHD en 30 controlepatiënten, die geen CHD of onderontwikkelde longen hadden, maar die wel een vergelijkbare intensive-care-behandeling na hun geboorte hadden ondergaan. Bij deze leeftijdgroep zijn de inspanningstesten uitgevoerd door middel van fietsergometrie met zuurstofmeting. Zowel de groep jongvolwassenen met CHD als de controlegroep scoorden onder de norm. Er werden bij dit onderzoek geen verschillen gevonden tussen beide groepen, waar het het duuruithoudingsvermogen, de mate van vermoeidheid en de mate van fysieke activiteit betreft. We concludeerden daarom dat niet alleen de restverschijnselen van CHD, maar ook de ademhalingsproblemen in de neonatale periode en de intensive-care-behandeling mogelijk bijdragen aan de uitkomsten op jongvolwassenleeftijd.

Deel 3 van dit proefschrift beschrijft de follow-up van kinderen die na hun geboorte behandeld zijn met extracorporele membraan oxygenatie (ECMO).

In **hoofdstuk 6** onderzochten wij de motorische ontwikkeling op de leeftijd van 5 jaar bij kinderen die behandeld zijn met ECMO. De kinderen werden behandeld in de twee officiële behandelcentra in Nederland: het Universitair Medisch Centrum St. Radboud in Nijmegen en het Erasmus MC - Sophia Kinderziekenhuis in Rotterdam. ECMO wordt vooral toegepast bij pasgeborenen met MAS (deze kinderen hebben meconium via het vruchtwater in de longen gekregen), CHD, sepsis (bloedvergiftiging) en PPHN (hierbij blijft de weerstand in de longvaten hoog waardoor er minder bloed naar de longen gaat). Alle 174 vijfjarigen die tussen 1993 en 2000 waren behandeld met ECMO werden opgeroepen en 149 kinderen (86%) werden daadwerkelijk onderzocht. Het follow-up programma bestond uit een medisch onderzoek, een kinderfysiotherapeutisch onderzoek met de MABC, een onderzoek door de ontwikkelingspsycholoog met de Revisie Amsterdamse Kinder Intelligentietest (RAKIT) en een gedragsvragenlijst (CBCL). Bij 49% van de kinderen werd een normale ontwikkeling in alle domeinen gevonden (MABC, RAKIT en CBCL). Kinderen met CHD, sepsis en PPHN scoorden op de MABC lager dan verwacht op basis van de normscores. Kinderen met MAS scoorden niet onder de norm. De meeste problemen werden wederom gevonden bij de balvaardigheden en bij het statische en dynamisch evenwicht. De handvaardigheden echter werden veelal volgens de leeftijdsnorm uitgevoerd. De scores op de RAKIT en de CBCL verschilden niet van de referentiescores. De totaalscore op de MABC, groeiparameters en CBCL

waren niet aan elkaar gerelateerd. Slechte scores op de MABC waren echter wel gerelateerd aan lage intelligentiequotiënten.

We concludeerden dat kinderen die als pasgeborenen zijn behandeld met ECMO last kunnen krijgen van problemen in hun ontwikkeling, vooral waar het de motoriek betreft. Naar onze mening is een multidisciplinair follow-up programma ook voor deze kinderen onontbeerlijk om de langetermijn morbiditeit samenhangend met de ECMO behandeling te evalueren.

Hoofdstuk 7 beschrijft een studie waarin we het duuruithoudingsvermogen van kinderen die na hun geboorte behandeld zijn met ECMO hebben onderzocht en waarbij we hebben gekeken hoe het duuruithoudingsvermogen zich ontwikkelt over de tijd. Voor deze studie zijn bij 120 kinderen op de leeftijd van 5, 8 en 12 jaar, 191 betrouwbare inspanningstesten afgenomen. We vormden 3 verschillende diagnosegroepen: kinderen met MAS, kinderen met een CHD en een groep overige diagnoses. Op de leeftijd van 5, 8 en 12 jaar scoorden de kinderen -gemiddeld genomen- onder de leeftijdsnorm. Bovendien bleek er een achteruitgang te zijn over de tijd. Bij deze studie was er geen verschil in uitkomst voor de verschillende diagnosegroepen. Vóór de inspanningstesten hebben wij alle ouders gevraagd hoe zij het duuruithoudingsvermogen van hun kinderen zouden beoordelen. Het bleek dat de ouders een goed beeld van het duuruithoudingsvermogen van hun kinderen hadden.

We adviseren daarom vroegtijdige sportdeelname of verwijzing naar een kinderfysiotherapeut, vooral als ouders zelf al problemen betreffende het duuruithoudingsvermogen van hun kinderen rapporteren.

In het laatste hoofdstuk, de **discussie,** beschrijven we onze belangrijkste bevindingen en geven we adviezen voor verder onderzoek.
De belangrijkste onderwerpen voor verder onderzoek zijn volgens ons:

- het onderzoeken of programma's met vroegtijdige kinderfysiotherapeutische interventie kunnen bijdragen aan een betere motoriek en/of een beter duuruithoudingsvermogen bij kinderen die geboren zijn met CHD of OA en bij kinderen die na hun geboorte behandeld zijn met ECMO
- het opzetten van (internationale) multi-center studies met grotere patiëntenaantallen. Gestandaardiseerde zorg en verzameling van data zijn hierbij belangrijk om een beter zicht te krijgen op risicofactoren voor een vertraagde motorische ontwikkeling
- het onderzoeken welke inspanningstesten (op de fiets of op de loopband) het meest geschikt zijn voor 12- en 18-jarige CHD en OA patiënten.

Abbreviations

AAP	American Academy of Pediatrics
ACCP	American College of Chest Physicians
AM	Activity Monitor
ANOVA	Analysis of Variance
ASD	Atrial Septal Defect
ATS	American Thoracic Society
AWD	Abdominal Wall Defect
BMI	Body Mass Index
BPD	Bronchopulmonary Dysplasia
BPM	Beats Per Minute
CA	Congenital Anomaly
CBCL	Child Behavior Checklist
CDH	Congenital Diaphragmatic Hernia
CI	Confidence Interval
CLD	Chronic Lung Disease
CPET	Cardiopulmonary Exercise Testing
DL_{CO}	Carbon Monoxide Diffusion Capacity
DL_{CO} /V_A	DL_{CO} corrected for alveolair volume
EA	Esophageal Atresia
ECMO	Extracorporeal Membrane Oxygenation
EEG	Electroencephalography
ERS	European Respiratory Society
FE_{NO}	Fraction of exhaled NO
FEV_1	Forced Expiration Volume in 1 second
FiO_2	Fraction of Inspired Oxygen
FSS	Fatigue Severity Scale
FVC	Forced Vital Capacity
GER	Gastro-esophageal Reflux
HFO	High Frequency Oscillation
HR	Heart Rate
ICU	Intensive Care Unit
IQ	Intelligent Quotient
LIFE-H	Life Habits Questionnaire

MABC	Movement Assessment Battery for Children
MAP	Mean Airway Pressure
MARS	Motion Artifact Reduction System
MAS	Meconium Aspiration Syndrome
MRI	Magnetic Resonance Imaging
NO	Nitric Oxide
NS	Not Significant
OI	Oxygenation Index
PaO_2	Partial Pressure of Oxygen in Arterial Blood
PAR-Q	Physical Activity Readiness Questionnaire
$PetCO_2$	End Tidal Carbon Dioxide
$PetO_2$	End Tidal Oxygen
PPH	Persistent Pulmonary Hypertension
PPHN	Persistent Pulmonary Hypertension of the Newborn
RAKIT	Revised Amsterdam Children's Intelligent Test
RER	Respiratory Exchange Ratio
RTI	Respiratory Tract Infections
SD	Standard Deviation
SDS	Standard Deviation Score
SE	Standard Error
SES	Socioeconomic Status
SF-36	Short Form-36
SGA	Small for Gestational Age
SIA	Small Intestinal Anomalies
SPSS	Statistical Package Social Sciences
SPO_2	Saturation of Peripheral Oxygen
TIS	Total Impairment Score
VA	Veno-Arterial
VAT	Ventilatory Anaerobic Threshold
VE/VCO_2	Ventilatory Equivalents for Carbon Dioxide Output
VE/VO_2	Ventilatory Equivalents for Oxygen Uptake
VO_2max	Maximal Oxygen Uptake
V/Q	Ventilation/perfusion
VSD	Ventricular Septal Defect
W_{peak}	Peak work load

Dankwoord

We ourselves feel that what we are doing is just a drop in the ocean.
But the ocean would be less because of that missing drop.

Mother Teresa

Het onderzoek -gepresenteerd in dit proefschrift- voelt aan als de kroon op de ruim 30 jaar werken in het Sophia Kinderziekenhuis. Op 1 april 2006 kon ik met mijn onderzoek aan de slag. Er is heel wat gebeurd sinds die dag. Ik heb het als een bijzondere en leerzame periode ervaren. In de afgelopen jaren heb ik veel steun en vertrouwen gekregen en er zijn dan ook veel mensen voor mij belangrijk geweest bij het tot stand komen van dit proefschrift. Een aantal van hen wil ik hier in het bijzonder bedanken:

De belangrijkste dank gaat uit naar alle kinderen en hun ouders die deel uitmaken van onze follow-up. Zonder jullie was dit proefschrift er niet geweest. Ik heb grote bewondering voor jullie doorzettingsvermogen en veerkracht.

Prof. dr. D. Tibboel, promotor.
Beste Dick, jaren geleden werd ik de kinderfysiotherapeut voor jouw afdeling: de chirurgische intensive care. Vanuit die setting raakte ik betrokken bij de chirurgische follow-up. Toen er zich een mogelijkheid voordeed tot het doen van onderzoek in het kader van de ECMO follow-up, voelde ik me aanvankelijk overvallen en verrast. Geweldig was jouw reactie toen ik weken later aangaf de uitdaging toch met beide handen aan te willen grijpen. Gelijk vanaf dat moment heb je me veel vertrouwen geschonken. Dick, ik ben de eerste fysiotherapeut die onder jouw leiding gaat promoveren en ben zeer vereerd dat je de klus met me aandurfde. De laatste jaren heb ik je op een andere manier leren kennen. Heel veel dank.

Dr. H. Meijers-IJsselstijn, copromotor.
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Dr. H.J.G. van den Berg-Emons, copromotor.
Beste Rita, vanaf het begin was jij vanuit de afdeling Revalidatie betrokken bij mijn onderzoek. Dank voor je inbreng, het zorgvuldig lezen van de artikelen en de steeds heldere feedback. Ik heb de samenwerking als heel waardevol ervaren. Ondertussen zijn we collega's en ik hoop dat de samenwerking dus nog langer door kan gaan.

Prof. dr. H. Stam, hoofd afdeling Revalidatie Geneeskunde en Fysiotherapie.
Beste Henk, ook jij bent vanaf het begin betrokken bij mijn onderzoek. Dank voor de gastvrijheid op je afdeling bij de metingen op het bewegingslab. Dank voor je duidelijke

en waardevolle commentaar bij mijn eerste artikelen en fijn dat je zitting nam in de kleine commissie.

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Eric Benda, hoofd afdeling Fysiotherapie.
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Collega's van de vakgroep kinderen van de afdeling Revalidatiegeneeskunde en Fysiotherapie.
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hebben. Annelies en Lianne, jullie hadden de weg al voor mij geëffend, fijn dat ik jullie om raad kon vragen. Nelleke, dank voor je steun tijdens de congressen van de NVFK, veel succes met je nieuwe studie, wat goed dat je voor jezelf hebt durven kiezen. Manon en Leontien, jullie waren geregeld mijn klankbord. Dank voor jullie geduldig luisteren en meedenken. Manon, ik ben super trots op je. Wat een doorzettingsvermogen. Hou vol! En Leontien: je project wordt vast geweldig, fijn dat ik jou hierin -samen met Annelies- kan begeleiden.

Leden van de chirurgische lange termijn follow-up. Het supportteam is uitgegroeid tot een geweldig multidisciplinair team; het is fijn jullie als collega's te hebben. Ik vind deze manier van zorgbieden aan kinderen en hun ouders een voorbeeld van hoe het eigenlijk overal in de gezondheidszorg zou moeten zijn.

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maakt, heb je geen tijd om oud te worden". Dus: of dat woordje "Young" nu wel of niet in onze naam blijft staan, laten we vooral enthousiast samen verdergaan.

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Publications
&
PhD portfolio summary

PUBLICATIONS

Hartman A, van der Cammen-van Zijp MH.
De zuigeling met een vergrote buikomvang.
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Hanekamp MN, Mazer P, van der Cammen-van Zijp MH, van Kessel-Feddema BJ, Nijhuis-van der Sanden MW, Knuijt S, Zegers-Verstraeten JL, Gischler SJ, Tibboel D, Kollée LA.
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Exercise testing of pre-school children using the Bruce treadmill protocol; new reference values.
Eur J Appl Physiol. 2010 Jan; 108 (2): 393-399

Mazer P, Gischler SJ, van der Cammen-van Zijp MHM, Tibboel D, Bax NMA, IJsselstijn H, van Dijk M, Duivenvoorden HJ.
Early developmental assessment of children with major non-cardiac congenital anomalies predicts development at the age of five years.
Dev Med Child Neurol, 2010 (in press)

van der Cammen-van Zijp MHM, Gischler SJ, Mazer P, van Dijk M, Tibboel D, IJsselstijn H.
Motor-function and exercise capacity in children with major anatomical anomalies: An evaluation at 5 years of age.
Early Human Development, 2010 (in press)

PHD PORTFOLIO SUMMARY

Summary of PhD training and teaching activities

Name PhD student:	M.H.M. van der Cammen - van Zijp
Erasmus MC Department:	Rehabilitation Medicine and Physical Therapy Intensive Care and Pediatric Surgery
Research School:	Erasmus MC
PhD period:	April 2006 - Oktober 2010
Promotor:	Prof. dr. D. Tibboel
Copromotoren:	Dr. H. Meijers-IJsselstijn Dr. H.J.G. van den Berg-Emons

	Year	Workload
Courses		
- Methodologie van patiëntgebonden onderzoek en voorbereiding subsidieaanvragen	2006	5 hours
- Biomedical English Writing and Communication	2008/2009	4 ECTS
- Research Integrity (BROK)	2009	2 ECTS
Presentations		
- Gross motor function measure: maat en meetlat bij cerebrale parese: ISBN-13:978-9076220192 Kinderartsenweek: "Zorg voor een kind met een beperking" (oral presentation)	2006	50 hours
- Idem	2007	8 hours
- Hernormering Bruce protocol Congres NVFK (oral presentation)	2008	40 hours
- Kinderen met ernstige anatomische aangeboren afwijkingen: motoriek en conditie Congres NVFK (poster)	2009	40 hours
International conferences		
- Congres European Society of Paediatric and Neonatal Intensive Care (ESPNIC). Verona; Two poster presentations, one oral presentation	2009	120 hours
- First International Workshop on Oesophageal Atresia. Lille; (poster)	2010	40 hours
Conferences		
- H.K.A. Visser-lezing	2006	2 hours
- Congres NVFK "Mama, ik ben zo moe"	2006	8 hours
- Recente ontwikkelingen in de zorg rondom prematuren	2007	3 hours
- Rehab on the move; towards interventions to improve physical activity and fitness of young people with physical disabilities	2008	3 hours
- Jubileumcongres NVFK	2010	8 hours
Other		
- Maandelijkse research bespreking kinderchirurgie	2008-2010	1 hour each
- Beroepsinhoudelijke besprekingen fysiotherapie (4 per jaar)	2006-2010	1 hour each
- Presentatie tijdens research bespreking afdeling Revalidatie geneeskunde en Fysiotherapie	2009	16 hours
- Presentatie tijdens research bespreking kinderchirurgie (3 maal)	2008-2010	8 hours each
- Multidisciplinair follow-up overleg (tweemaal per maand)	2006-2010	1 hour each
- Begeleiding afstudeerproject medisch student	2009	90 hours
- Begeleiding stagiaires kinderfysiotherapie	2006-2010	20 hours each year
	Total workload =	843 hours

Sophia Kinderziekenhuis
afdelingen
Revalidatie Geneeskunde en Fysiotherapie
Intensive Care Kinderen en Kinderchirurgie

Erasmus MC
Universitair Medisch Centrum Rotterdam

Normwaarden Bruce protocol voor kinderen van 4 t/m 13 jaar

Monique van der Cammen-van Zijp, kinderfysiotherapeut

Bruce protocol			
stap	snelheid km/uur	helling %	duur min
I	2,7	10	3
II	4	12	3
III	5,4	14	3
IV	6,7	16	3
V	8	18	3
VI	8,8	20	3
VII	9,6	22	3

Achtergronden en nadere details zijn te vinden in de volgende artikelen:

Exercise testing of pre-school children using the Bruce treadmill protocol; new reference values. Van der Cammen-van Zijp MH, IJsselstijn H, Takken T, Willemsen SP, Stam HJ, Tibboel D, van den Berg-Emons RJ. Eur J Appl Physiol 2010;108:393-399

Exercise capacity in Dutch children; new reference values for the Bruce treadmill protocol. Van der Cammen-van Zijp MH, van den Berg- Emons RJ, Willemsen SP, Stam HJ, Tibboel D, IJsselstijn H. Scand J Med Sci Sports 2010;20:e130-e136

Algemeen

De kinderen zijn tussen juli 2006 en maart 2008 getest op verschillende scholen in Zuidwest Nederland. Criteria voor maximale inspanning: hartfrequentie ≥ 185 slagen per minuut of ernstige verslechtering van de coördinatie.

Jongens en meisjes van 4 en 5 jaar oud (n=53; 25 jongens en 28 meisjes)

Procedure: de kinderen hebben tijdens het lopen de leuning van de loopband licht vastgehouden om het evenwicht te bewaren. Het was de kinderen niet toegestaan om op de leuning te hangen.

Tabel 1 volhoudtijd jongens en meisjes 4 en 5 jaar oud

geslacht	leeftijd	p 5	p 10	p 25	p 50	p 75	p 90	p 95
jongens	4,00	5,55	6,14	7,14	8,25	9,36	10,36	10,96
	4,25	5,94	6,54	7,54	8,65	9,76	10,76	11,35
	4,50	6,34	6,94	7,94	9,05	10,16	11,15	11,75
	4,75	6,74	7,34	8,33	9,44	10,55	11,55	12,15
	5,00	7,14	7,73	8,73	9,84	10,95	11,95	12,55
	5,25	7,53	8,13	9,13	10,24	11,35	12,35	12,94
	5,50	7,93	8,53	9,53	10,64	11,74	12,74	13,34
	5,75	8,33	8,92	9,92	11,03	12,14	13,14	13,74
meisjes	4,00	7,76	8,20	8,92	9,73	10,54	11,27	11,70
	4,25	7,86	8,29	9,02	9,83	10,64	11,36	11,80
	4,50	7,95	8,39	9,12	9,92	10,73	11,46	11,89
	4,75	8,05	8,48	9,21	10,02	10,83	11,55	11,99
	5,00	8,14	8,58	9,31	10,12	10,92	11,65	12,09
	5,25	8,24	8,68	9,40	10,21	11,02	11,75	12,18
	5,50	8,34	8,77	9,50	10,31	11,11	11,84	12,28
	5,75	8,43	8,87	9,59	10,40	11,21	11,94	12,37

Leeftijd in jaren; volhoudtijd in minuten
SD volhoudtijd jongens = 1,64 minuten
SD volhoudtijd meisjes = 1,20 minuten
SD = standaarddeviatie; p = percentiel

Jongens en meisjes van 6 t/m 13 jaar oud (n=267; 133 jongens en 134 meisjes)

Procedure: de kinderen mochten de leuning niet vasthouden behalve gedurende 5 seconden tijdens de veranderingen van snelheid en hellingshoek.

Tabel 2 volhoudtijd jongens 6 t/m 13 jaar oud

leeftijd	p 5	p 10	p 25	p 50	p 75	p 90	p 95
6,0	7,9	8,4	9,2	10,1	11,0	11,9	12,3
6,5	8,3	8,8	9,6	10,5	11,4	12,2	12,7
7,0	8,7	9,1	10,0	10,9	11,8	12,6	13,1
7,5	9,0	9,5	10,3	11,2	12,1	12,9	13,4
8,0	9,4	9,9	10,7	11,6	12,5	13,3	13,8
8,5	9,7	10,2	11,0	11,9	12,8	13,6	14,1
9,0	10,0	10,5	11,3	12,2	13,1	14,0	14,4
9,5	10,3	10,8	11,6	12,5	13,4	14,2	14,7
10,0	10,5	11,0	11,8	12,8	13,7	14,5	15,0
10,5	10,7	11,2	12,0	12,9	13,8	14,7	15,2
11,0	10,9	11,4	12,2	13,1	14,0	14,8	15,3
11,5	11,0	11,5	12,3	13,2	14,1	14,9	15,4
12,0	11,1	11,6	12,4	13,3	14,2	15,0	15,5
12,5	11,2	11,7	12,5	13,4	14,3	15,1	15,6
13,0	11,2	11,7	12,6	13,5	14,4	15,2	15,7

Leeftijd in jaren; volhoudtijd in minuten
SD volhoudtijd = 1,3 minuten
SD = standaarddeviatie; p = percentiel

Leeftijd 6 en 7 jaar: 37 jongens
Leeftijd 8 en 9 jaar: 35 jongens
Leeftijd 10 en 11 jaar: 29 jongens
Leeftijd 12 en 13 jaar: 32 jongens

Tabel 3 volhoudtijd meisjes 6 t/m 13 jaar oud

leeftijd	p 5	p 10	p 25	p 50	p 75	p 90	p 95
6,0	6,9	7,4	8,2	9,2	10,1	11,0	11,5
6,5	7,2	7,8	8,6	9,5	10,5	11,3	11,9
7,0	7,6	8,1	9,0	9,9	10,9	11,7	12,2
7,5	8,0	8,5	9,4	10,3	11,3	12,1	12,6
8,0	8,4	8,9	9,7	10,7	11,6	12,5	13,0
8,5	8,7	9,2	10,1	11,0	12,0	12,8	13,3
9,0	9,0	9,5	10,4	11,3	12,3	13,1	13,6
9,5	9,3	9,8	10,6	11,6	12,5	13,4	13,9
10,0	9,5	10,0	10,8	11,8	12,7	13,6	14,1
10,5	9,6	10,1	10,9	11,9	12,8	13,7	14,2
11,0	9,6	10,1	10,9	11,9	12,8	13,7	14,2
11,5	9,6	10,1	10,9	11,9	12,8	13,7	14,2
12,0	9,5	10,0	10,9	11,8	12,8	13,6	14,1
12,5	9,4	9,9	10,8	11,7	12,7	13,5	14,0
13,0	9,3	9,8	10,7	11,6	12,6	13,4	13,9

Leeftijd in jaren; volhoudtijd in minuten
SD volhoudtijd = 1,4 minuten
SD = standaarddeviatie; p = percentiel

Leeftijd 6 en 7 jaar: 33 meisjes
Leeftijd 8 en 9 jaar: 26 meisjes
Leeftijd 10 en 11 jaar: 48 meisjes
Leeftijd 12 en 13 jaar: 27 meisjes

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