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Deterioration of exercise capacity after neonatal extracorporeal membrane oxygenation

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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: 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 between 2001 and 2010. 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.

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 is recommended; especially when either the parents or the children themselves report impaired exercise capacity.

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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 neonates who all received veno-arterial (VA) ECMO support between January 1992 and July 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. The Medical Ethical Review Board Erasmus MC declared to have no objection against implementation of this research project (MEC-2010-179). Parents of the participating children gave written permission for publication of the results of our follow-up.

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 before and after bronchodilation with salbutamol. A dry rolling seal spirometer (Jaeger,Hoechberg, Germany) was used according to European Respiratory Society (ERS) criteria.[13] Three forced vital capacity (FVC) maneuvers were performed and the best values of forced expiratory volume in 1 s (FEV1) and FVC were recorded. The children had been instructed to stop short-acting β2-agonists 8 hours and long-acting β2-agonists 24 hours before assessment.

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 reductionsystem), 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 FiO2)/PaO2] 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 FEV1, SDS FEV1/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 July 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=10), 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 did not 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 Test p =0.027).

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 test p = 0.007 and p = 0.012 respectively). The final analysis concerned 191 exercise tests performed by 120 children (68% of all survivors) (fig.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 I (see page 13). Inhaler medication was used by 3.4% of the 5-year-olds, 10.4% of the 8-year-olds, and 5.9% of the 12-year-olds.

At time of follow-up, the mean SDS FEV1 was significantly below zero at ages 5, 8 and 12. This also applies to mean SDS FEV1/FVC at ages 8 and 12. The mean change in FEV1 from baseline was 8.6%, 6.3%, and 7.2% at 5, 8, and 12 years, respectively. We observed significant reversibility of airflow obstruction (i.e. a change in FEV1 > 11% [22]) in 13, 12, and 6 children aged 5, 8, and 12 years, respectively. The characteristics at time of follow-up of the children of the study group are presented in Table II.

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 $p < 0.001$). SD's of the mean SDS endurance time at the three measurement points were 1.06, 1.18 and 1.18 respectively. The mean difference between age 8 and 5 was -0.5 (95% CI: -0.9 to -0.2); that between ages 12 and 8 was -0.4 (95% CI: -0.8 to 0.0). 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 10th and 90th 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. Sixty-two children had at least 2 measurements at different ages. All together there were 80 paired measurements. Thirty-four of these paired measurements showed a deterioration of more than 1 SDS. In 41 paired measurements the change in SDS ranged between -1 and +1 (suggesting no significant change in exercise capacity). Improvement of at least 1 SDS was observed 5 times. 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 FEV1; SDS FEV1/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 ($p = 0.002$).

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. Parents' estimations of the children's levels of exercise capacity positively correlated with the endurance SD scores. None of the clinical characteristics correlated with exercise tolerance.

Fourteen children did not perform the exercise test because of neurological problems or behavioural problems. These 14 children seemed to be the sickest individuals as reflected by the longer duration of ventilation, and should therefore be considered as poor outcome. Boykin and colleagues tested exercise capacity of 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 presumably included more children with initial pulmonary hypoplasia and residual pulmonary sequelae, because Boykin and colleagues studied MAS patients only, who have intrinsically normal lungs.

Hamutcu and colleagues showed that 48 children (mean age 11.1 years), treated with ECMO for various conditions, including MAS and CDH had lower peak oxygen consumption than healthy age-matched controls.[9] Differences in protocol hamper comparison of the results. Nevertheless, we would like to point out that the oxygen desaturation (SPO2 < 90%) observed during exercise in almost 25% of the ECMO-treated children was not observed in any of our participants. Other than Hamutcu and colleagues, 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. [23] 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).[24] In a study of Peetsold and colleagues 36 of 53 survivors of CDH who had not received ECMO treatment (mean (SD) age 11.9 (3.5) years) reliably performed the Bruce treadmill test.[25] In most of them the exercise capacity agreed with the reference values of Binkhorst et al. established in 1987.[26] There was a positive but small correlation between the SDS VO2Max and the SDS FEV 1 (R^2 = 0.27; p = 0.001). In our study the correlation between maximal endurance time and SDS FEV1 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.[27] As bronchopulmonary dysplasia was over-represented in the prematurely borns, exercise capacity of participants with and without bronchopulmonary dysplasia was compared. A significant difference was not found.

The question is whether brochodilators would have improved our results. We do not think so because we only observed a significant reversibility of airway obstruction in a small number of children (n=31). In 20 of them (64.5%) lung function assessment with bronchodilation was performed prior to the exercise test. So, better performance during the exercise test could have been expected in 11 children only.

Earlier we found balance skills problems in five-year-old children treated with neonatal ECMO [7]. These 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 explanatory factor could be lack of exercise, however reported sports participation had increased at 8 years; this seems to contradict lack of exercise as explanatory factor. At 12 years, on the contrary, 26% of the 12-year-old children did not report sports participation.

Regrettably we have no data from CT scans, so progressive fibrosis as reason of deterioration over time cannot be ruled out.

In our study group 18 patients had CDH with pulmonary hypertension and 20 were treated with ECMO for persistent pulmonary hypertension. In both conditions, pulmonary vasoreactivity may persist and result in ventilation-perfusion mismatch. We did not perform cardiac evaluations to confirm this speculation. For CDH patients ventilation-perfusion mismatch has been described previously.[28]

In contrast to the UK Collaborative ECMO trial [1] our study was not set up as a randomized study with controls suffering from severe neonatal cardiorespiratory failure who were treated conventionally. With only two ECMO centers in the Netherlands, covering a relatively small geographical area, the large majority of neonates with similar severity of illness who are not born prematurely (i.e. born after 34 weeks gestation with birth weight > 2000 grams) are treated with ECMO. Therefore, it was not possible to obtain a substantial number of children who survived without ECMO to serve as a control group since one wants to avoid using historical data. Recruiting controls from other countries with less easy access to ECMO treatment could have been an option. However, differences in the definitions of optimal care for specific diseases and differences in quality of care will almost certainly create bias.

At follow-up at 7 years of age the conventionally treated children in the UK Collaborative ECMO trial had more respiratory morbidity than had the ECMO-treated.[3] Thus, we speculate that imaginary disease-matched controls in our study would have performed worse than the ECMO-treated children.

Another possible limitation of our study is the lack of healthy controls. We do not think that this invalidates our findings, as our study aimed to prospectively evaluate exercise capacity with advancing age. 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 is recommended; especially when either the parents or the children themselves report impaired exercise capacity.

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Table I: 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)
Remaining, 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, median (Range)	24 (4-600)	27 (5-398)	25 (5-288)	20 (4-600)	24 (5-41)
Time on ECMO, hours, median (Range)	132 (24-510)	131 (24-369)	133 (48-347)	172 (61-510)	140 (58-220)
Ventilatory support, days, median (Range)	12 (1-130)	11 (1-70) *	13 (5-40)	20 (8-130)*	9 (6-50)
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 number (%) of patients or mean (SD) unless stated otherwise

* Mann-Whitney Test, p = 0.027 difference in ventilatory support between children who were unable to perform exercise test and participants

§ Mann-Whitney Test p = 0.007 difference in oxygen support between children without maximal performance and participants

‡ Mann-Whitney 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 = extra corporeal membrane oxygenation; NO = nitric oxide

Table II: characteristics at follow-up at ages 5, 8 and 12 years

	5 years	8 years	12 years
n	90	67	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 FEV1	-0.54 (1.11)*	-0.64(1.29)*	-1.11 (1.54)*
SDS FEV1/FVC	-0.11 (1.44)	-0.70 (1.15)*	-1.03 (1.22)*

Data shown are number (%) of patients or mean (SD)

*one sample T-test: mean value significantly different from zero: $P \leq 0.001$

CDH = congenital diaphragmatic hernia

MAS = meconiumaspiration syndrome

SDS = standard deviation score

FEV1 = forced expiratory volume in 1 s

FVC = forced vital capacity

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

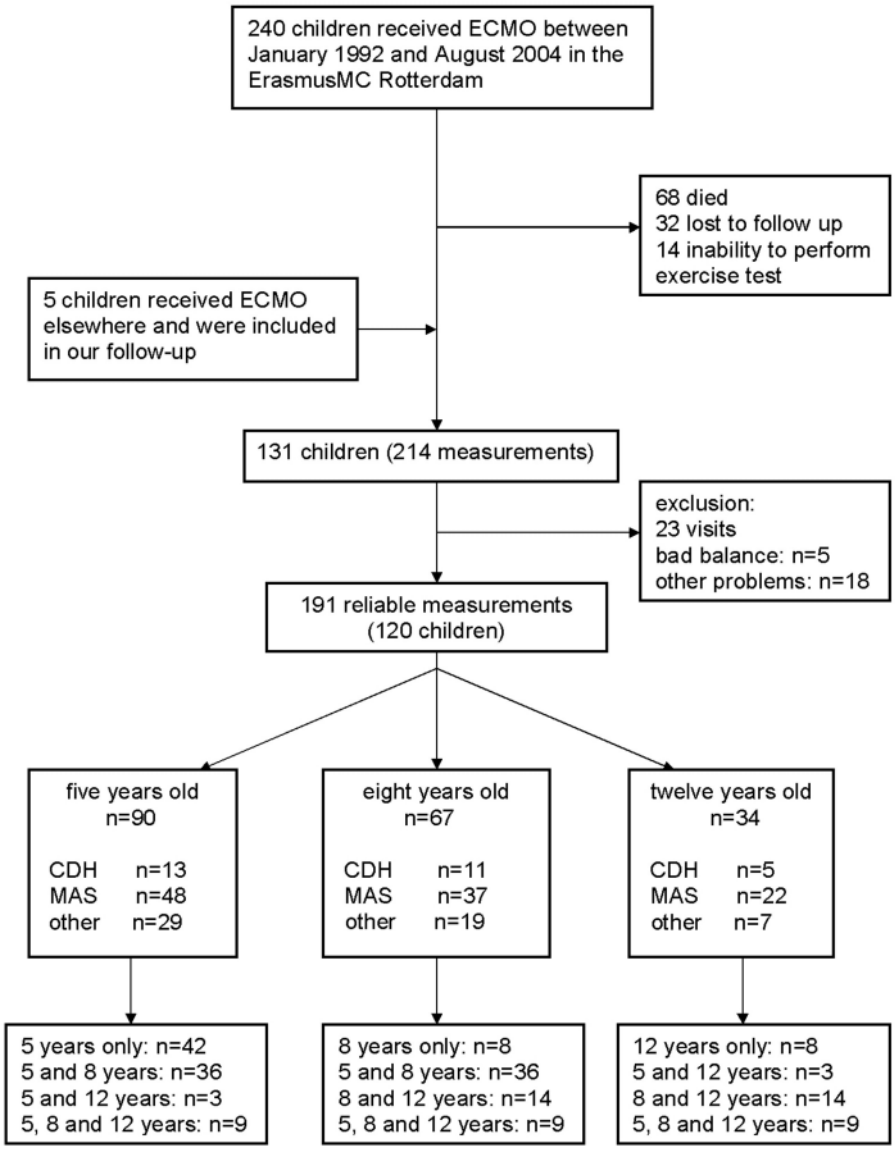
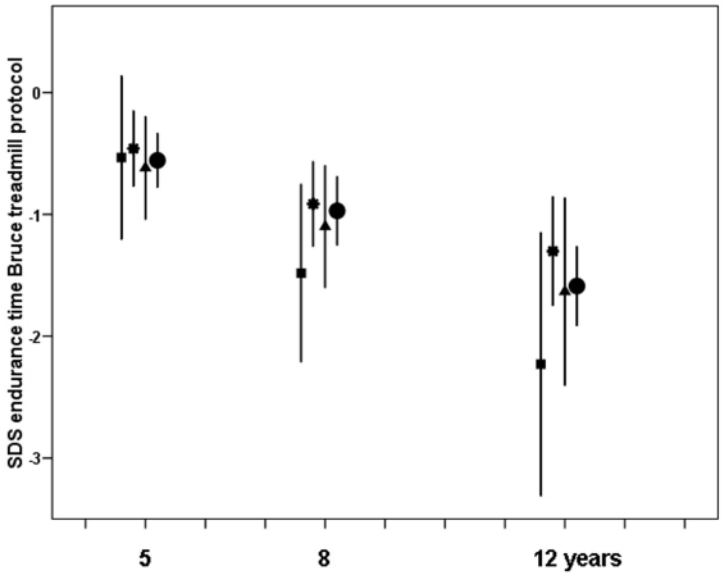


Figure 2: Exercise capacity at the different ages



Data shown are ANOVA estimates of mean values with 95% confidence intervals

squares: CDH asterisks: MAS triangles:remaining group circles: total group