Early motor development and exercise capacity association in children with a congenital heart disease: An explorative study

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ABSTRACT

Background:. Several studies report a high prevalence of abnormal cerebral findings in newborns with a congenital heart disease (CHD), frequently resulting in delayed motor development. Additionally, reduced exercise capacity is often observed in children with CHD and both motor development and exercise capacity decline with increased severity. As peak exercise capacity is a strong predictor for mortality, early identification is of great clinical value. However, assessment of exercise capacity can only be objectified by exercise testing from approximately the age of 6. Motor development outcomes however, seems to be an independent predictor of exercise capacity and may be used as an early predictor of decreased exercise capacity.

Aim: The primary aim of this study is to determine whether there is an association between motor development at the age of 3.5 and exercise capacity between 6 and 7 years. Additionally, association between motor development and exercise capacity between 6 and 7 will be determined. Motor development change over time will also be described. Lastly, we will explore whether exercise capacity is influenced by clinical characteristics.

Methods: Pediatric patients with various types of CHD from the Wilhelmina Children's Hospital in Utrecht were recruited. Motor development was tested with the MABC-2 at 3.5 years and BOT-2 and exercise capacity was assessed between 6 to 7 years, respectively. Correlations were determined to assess associations and univariate analysis was applied to determine the influence of clinical characteristics on exercise capacity.

Results: Thirty-five patients participated in this study. A weak correlation was found between motor development at 3.5 years and peak exercise between 6 and 7 years. Correlation between motor development and peak exercise capacity between 6 and 7 years was moderate. Motor development change over time was high. No clinical characteristics were significantly related

to peak exercise capacity.

Conclusion and key findings: Only a weak correlation was found, with no characteristics related to peak exercise capacity. Motor development was highly variable over the course of three years and consequently extensive follow-up should be part of usual care in patients with CHD. Future research should examine the association in a larger cohort of patients with CHD.

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INTRODUCTION

Congenital heart defects (CHD) are the most common congenital disorders in newborns [1] and leading causes of infant death from birth defects [2]. CHD is defined as "*a gross structural abnormality of the heart or intrathoracic great vessels that is actually or possibly of functional significance*" [3]. Approximately 25% of all CHD's are considered to be critical CHD (CCHD) and require surgical correction within the first year of life [4]. Due to progression in pediatric and interventional cardiology, improvement of cardiac surgery and enhanced intensive care management [5–7], survival rate among all CHD severity categories has increased spectacular beyond 85% over the past few decades [7,8]. However, multiple studies have reported a high prevalence of prenatal and postnatal perioperative abnormal cerebral findings (e.g. brain delay/damage), especially in those with moderate and severe lesions [9–14]. As a consequence, children with CHD frequently demonstrate a delayed motor development [15–20], even after a solitary surgical intervention [21]. Although motor development outcomes in CHD can range from normal motor development to severe motor delays, type and severity of CHD appears to be an important predictor for level of neurodevelopmental delay [15,22,23] and therefore distinction between subtypes is of great clinical relevance. These neurodevelopmental delays are concerning in relation to long-term outcomes of these patients as they are a potential risk for future limited physical achievements, physical inactivity [24–27] and consequently decreased physical fitness [28–30]. However, motor development in these children is often merely assessed cross-sectionally on one occasion during early life and without associations with motor development during school age [31–33], making it difficult to detect changes over time and provide parents with answers regarding the expectations of their child with a CHD.

In school aged children with a CHD, reduced exercise capacity is a frequently observed

limitation [28–30]. Multiple reviews indicate a significant decrease of peak exercise capacity in children and adolescents with CHD, compared to healthy controls [34 35] in which the number of surgical interventions is related to the severity of the CHD and negatively influences peak exercise capacity [36]. As peak exercise capacity is a strong predictor for mortality, morbidity and hospitalization in adults with CHD [37–39], early identification of children at risk is of great clinical value. Since cardiopulmonary exercise testing is feasible and reliable from approximately 6 years of age and motor development outcomes seems to be an independent predictor of exercise capacity and physical activity during early childhood, motor developmental outcomes may be used as an early predictor of decreased exercise capacity [40]. Motor development, opposed to exercise capacity, can already be valid determined within the first months after birth. A clinical relevant motor development assessment age is around 3.5 years as children are more cooperative, differences with peers becomes more evident and might be the ideal time to intervene if necessary. Accordingly, motor development assessment at 3.5 years of age might be useful to early identify children at risk for decreased exercise capacity during childhood. To our knowledge, no studies have been performed regarding possible associations between early motor development and exercise capacity during childhood in patients with (C)CHD.

Therefore, the primary aim of this study is to explore whether there is an association between motor development at the age of 3.5 years and peak exercise capacity between 6 and 7 years in children with moderate to severe CHD. If the association is strong, interventions at an early age might be warranted, along motor function, to improve exercise capacity to limit potential risk for future reduced physical achievements.

METHODS

Study population

Pediatric patients with various severity types of CHD from the Wilhelmina Children's Hospital (WCH) in Utrecht were recruited for the study since 2011. Around 30-35 children with serious (e.g. moderate or great complexity) CHD are born in the WCH each year. In order to be eligible to participate, a patient must have 1) underwent surgery requiring the use of cardiopulmonary bypass before the age of 6 months, or 2) had a complicated postoperative trajectory, resulting in necrotizing enterocolitis or total parenteral nutrition, or 3) underwent a therapeutic heart catheterization and was in a resuscitation setting (not per definition as a result from the heart catheterization). Patients with an additional syndrome verified by genetic testing (such as Trisomy 21 or 22q11d.) were excluded since possible diminished motor development and/or peak exercise capacity in these patients is not merely related to their CHD.

Design and protocol

The study was a explorative cohort study with predefined measurement points as described in the 'Hart-op-Weg' protocol (see Figure 1) which started in 2011 and is part of usual care. In this study, our main focus was on motor development at the age of 3.5 years and exercise capacity at the age between 6 and 7 years. However, motor development between 6 and 7 years was also taken into account to determine motor developmental changes over time as variation between patients (within subtypes) is high. Baseline and clinical factors were collected to determine whether they might influence exercise capacity. Results for motor development were depicted as one overall total motor score and by CHD-subtype as severe subtypes seems more affected.

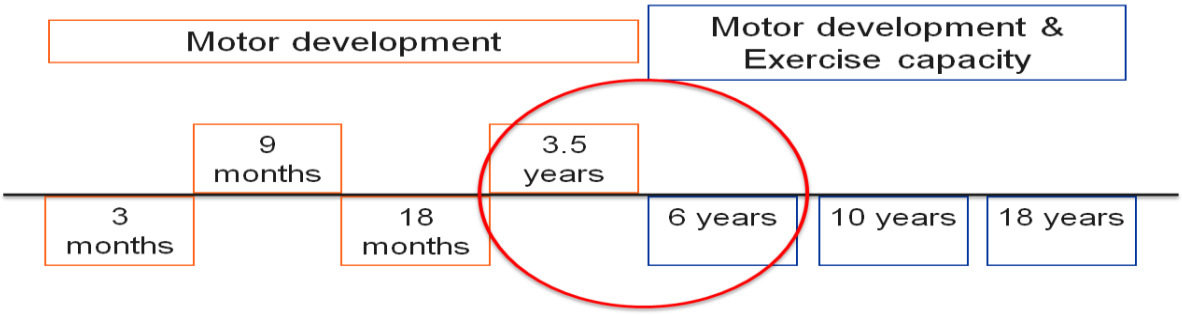

Figure 1. *Overview ''Hart-op-Weg'' protocol. For this study, we focus on the measurements taken at 3.5 and 6-7 years as circled in red.*

Motor development at 3.5 years

At 3.5 years, children visited the Child Development and Exercise Centre of the WCH at which the Movement Assessment Battery for Children-2 (MABC-2) was administered. With the test, three different domains of motor development are examined; 1) manual dexterity, 2) ball skills and 3) balance [41]. Raw scores are converted into scale scores based on age-specific normative data. Total test score is computed as the sum of the scale scores and is notated as norm score, of which percentile scores are calculated [41]. Normative values were used to score the child [42].

Motor development between 6 and 7 years

Between the age of 6 and 7 years, children visited the Child Development and Exercise Centre of the WCH at which the Bruininks-Oseretsky Test of Motor Proficiency-2 (BOT-2) was administered, which examines gross motor skills with five subtests and fine motor skills with three subtests. Items are scored on performance of each task [43]. The result of the test is an overall measure of motor proficiency and additionally scores are provided in four subscales; 1) fine manual control, 2) manual coordination, 3) body coordination and 4)

strength/agility [43]. Normative values were used to score the child [44].

Maximal exercise test by cardiopulmonary exercise test between 6 and 7 years

In addition to the BOT-2, a cardiopulmonary exercise test (CPET) was sequentially performed. The CPET was performed on a pediatric electronically braked upright cycle ergometer (Lode Corrival, The Netherlands). An incremental exercise protocol was applied according to the Godfrey protocol [45]. The protocol consists of three minutes of rest in order to measure rest parameters, followed by three minutes of cycling without workload and continues with a gradual increase of workload until exhaustion on 60-80 rotations per minute (RPM). After exhaustion, children were asked to perform a cool-down for three to five minutes. In order to measure breath-by breath respiratory gas analyses, participants breathed into a face-mask (Carefusion, Hans Rudolph Inc., USA) connected to a flow meter and a calibrated metabolic cart (Ergostik, Geratherm Respiratory, Germany). A 10-lead electrocardiographic recording system (AMEDTEC ECG Pro, AMEDTEC Medizintechnik Aue GmbH, Germany) continuously recorded and monitored heartrate. A pulse oximeter with forehead probe was used for continuous measurement of arterial oxygen saturation (Masimo Rad 8, Masimo bv, The Netherlands). Normative values for children of the age of 8 years were applied to calculate percentage of predicted [46], as we do not have published normative values, however most values are comparable in children between 6 and 7 years old.

Baseline and clinical characteristics

The following baseline and clinical characteristics were retrospectively collected from the patient's medical charts; 1) demographics and anthropometrics (e.g. gender, age, weight, height and body mass index (BMI)), 2) type of CHD, 3) whether they were born prematurely (< 37 weeks of gestational age), 4) number of surgery's (including re-surgery due to complications) and therapeutic heart catheterizations, 5) complicated postoperative trajectory

(defined as necrotizing enterocolitis or total parenteral nutrition), 6) open sternum postoperative, 7) duration of hospitalization (IC and medium care/ward), 8) duration of mechanical ventilation, 9) if a child has been resuscitated and 10) if a child had a pacemaker.

Statistical analysis

First, data was checked for normal distribution by visual inspection and statistical testing with the Shapiro-Wilk test. Missing data was described and pairwise or listwise deleted. Data was presented based on type and distribution. For continuous variables, mean and standard deviation where used when data was normally distributed and median and interquartile range were used when data was non-normally distributed. For categorical variables, data was presented as frequencies with percentage. To determine a possible association between motor development at 3.5 years old and exercise capacity between 6 and 7 years old, a Pearson correlation was determined between total motor score of the MABC-2 and peak exercise capacity (VO_2-peak/kg). We hypothesize to find at least a strong correlation ($\geq$0.7) [47]. Due to the number of included patients a univariate analysis was necessary to determine whether baseline and clinical factors had a significant influence on exercise capacity between 6 and 7 years. For determining the consistency and change of motor development over time, a Pearson correlation was determined between total motor development scores from the MABC-2 and BOT-2. Subsequently, Z-scores were calculated for both total motor development scores and where categorized as below -2 Z-scores, between -2 and -1, between -1 and 0 and above 0 and differences between Z-scores were calculated. A Z-score change greater than 1 was needed to be deemed a real statistical and clinical relevant change.

Sample size calculation

Although this study has an explorative design, a sample size calculation was performed. The main outcome is a correlation between total motor development at 3.5 years old and peak

exercise capacity between 6 and 7 years. Although a strong correlation ($r \geq 0.7$) is needed, we also want to be able te detect a moderate correlation $r=0.5$. Consequently, a two tailed alpha of 0.05 with a power of 0.95 gives a sample size of 46 [48] patient needed for the study.

RESULTS

A total of 35 patients with three different types of CHD participated in this study (see Table 1). In total, 30 out of 35 MABC-2 tests were completed at 3.5 years of age, 33 out of 34 BOT-2 tests completed between 6 and 7 years and 25 out of 32 exercise tests were considered as maximal effort (respiratory exchange ratio > 1.0). All none-completed motor development tests (n=5) were due to a reduced attention span and/or unwillingness to perform the task. One BOT-2 was not performed as the appointment was not planned. The three exercise tests that were not performed was due to tiredness of the patient after the BOT-2 or inability to plan the BOT-2 and exercise test sequentially.

Table 1 Patient and clinical characteristics

Gender (male/female)	**20/15 (57.1%/42.9%)**
Disease type	
Fontan / Single Ventricle Physiology	4 (11.4%)
Transposition of the Great Arteries	16 (45.7%)
Tetralogy of Fallot	15 (42.9%)
Born prematurely	8 (22.9%)
Total surgeries	1 (range 1-5)
Total therapeutic heart catheterizations	1 (range 0-4)
Delayed sternum closure	9 (25.7%)
Days open sternum	0 (range 0-5)
Total days on intensive care unit	9 (range 2-70)
Total days on regular ward	15 (range 3-98)
Total days of mechanical ventilation	5 (range 1-19)
Resuscitated	2 (5.7%)
Pacemaker	1 (2.9%)

Data presented as median (range) or frequency (percentage).

Correlation between total motor development score of the MABC-2 at 3.5 years and peak exercise capacity between 6 to 7 years was weak and non-significant (see Table 2 for *r* and P values). A moderate significant correlation was found between the total motor development score of the BOT-2 between 6 and 7 years and peak exercise capacity between 6 and 7 years.

Table 2 *Correlations between motor development at 3.5 years (MABC-2), motor development between 6 and 7 years (BOT-2) and peak exercise capacity (VO_2-peak) between 6 and 7 years*

	R-value	p-value
MABC-2 with VO_2-peak	-0.280	0.232
BOT-2 with VO_2-peak	0.497	0.016*
MABC-2 with the BOT-2	0.212	0.279

*=significant at 0.05 level (2-tailed). Abbreviations: R, correlation coefficient; p, probability value; MABC-2, Movement Assessment Battery for Children-2; VO_2-peak, exercise capacity at peak in millilitre per kilogram per minute; BOT-2, Bruininks-Oseretsky Test of Motor Proficiency-2

For comparison of motor development scores between 3.5 years of age and 6 to 7 years, 28 tests were available. There was a weak correlation between total motor development scores of the MABC-2 and BOT-2. A total of seven and six children were classified as at risk for or having delayed motor development for the MABC-2 at 3.5 years of age and the BOT-2 between 6 to 7 years, respectively. When describing the change over time, ten children had a lower motor development at 6 years then at 3.5 years and nine children had improved their motor development between 3.5 and 6 years. The last nine children did not change their motor development score between 3.5 and 6 years. See Table S1 for a detailed overview of the total motor development change over time and Table 3a & b for full motor development scores (both total score as per diagnosis).

Table 3a *Motor development results of the MABC-2 at the age of 3.5 years depicted as total and per diagnosis CHD*

	Total (n=30)	TGA (n=14)	TOF (n=12)	SVP (n=4)
Age at test	3.56 (3.54 – 3.69)	3.62 (3.55 – 3.69)	3.63 (3.54 – 3.68)	3.50 (3.48 – 3.50)
Posting Coins Item SS	10 (9 – 12)	9.5 (9 – 11.25)	10.5 (9 – 12)	11.5 (8.75 – 12.75)
Threading Beads Item SS	9.91 (2.82)	9.57 (2.14)	10.42 (3.78)	10.75 (2.99)
Drawing Trail Item SS	10 (7.75 – 11)	8.5 (5.75 – 10)	10 (9 – 11.75)	10.5 (10.0 – 13.25)
Manual Dexterity CS	9 (8 – 11)	8.5 (7.75 – 10.25)	10 (8 – 12.5)	11.5 (7.75 – 16.75)
Catching Beanbag Item SS	9.58 (2.85)	9 (2.80)	10 (2.09)	8.75 (4.86)
Throwing Beanbag Item SS	8 (6.5 – 10)	8 (5 – 10.50)	8 (7 – 9.5)	10 (7 – 13)
Aiming & Catching CS	9 (2.42)	8.71 (2.73)	8.67 (1.50)	9.25 (3.78)
One-Leg Balance Item SS	9 (8 – 11)	9.5 (8 – 11)	9 (8 – 11)	9.5 (8.25 – 10.75)
Walking Heels Raised Item SS	10.3 (2.86)	10.14 (2.91)	10.25 (2.86)	11 (3.37)
Jumping on Mats Item SS	10 (7 – 11)	10.5 (7 – 11)	10 (7 – 11)	9.5 (5.75 – 11.75)
Balance CS	9 (8 – 11)	9 (8 – 11)	9 (7.25 – 11.5)	9.5 (6.75 – 14.5)
Total Motor CS	9.30 (2.52)	8.79 (2.64)	9.50 (2.54)	10.50 (2.08)

Mean scores for the Movement Assessment Battery for Children is 10 with a SD of 3. Data presented as mean (SD) or median (25^{th} – 75^{th} percentile) Abbreviations: MABC-2, Movement Assessment Battery for Children-2; TGA, Transposition of the Great Arteries; TOF, Tetralogy of Fallot; SVP, Single Ventricle Physiology; SS, Standard Score; CS, Composite Score.

Table 3b *Motor development results of the BOT-2 at the age of 6.0 years depicted as total and per diagnosis CHD*

	Total (n=33)	TGA (n=16)	TOF (n=13)	SVP (n=4)
Age at test	6.39 (0.31)	6.41 (0.28)	6.39 (0.36)	6.40 (0.26)
Fine Motor Precision	15.6 (4.50)	16.56 (4.49)	14.5 (4.12)	16.5 (6.14)
Fine Motor Integration	13.7 (3.90)	14.6 (4.02)	13.2 (4.24)	12.0 (2.16)
Fine Manual Control SS	49.2 (8.87)	51.4 (8.51)	47.2 (9.66)	48.5 (8.70)
Manual Dexterity	14.6 (4.08)	15.25 (3.59)	14.8 (4.53)	12.0 (4.97)
Upper-Limb Coordination	12.4 (4.42)	12.5 (4.31)	12.3 (5.31)	11.75 (2.87)
Manual Coordination SS	46.3 (8.32)	47.0 (7.48)	46.9 (9.99)	42.0 (7.44)
Bilateral Coordination	15.0 (3.92)	15.13 (3.22)	14.9 (4.60)	15.25 (5.68)
Balance	14 (10 – 16)	15.5 (10 – 16.75)	13 (10 – 15)	14.5 (11 – 15)
Body Coordination SS	47.3 (8.25)	47.94 (8.20)	46.9 (8.87)	47.5 (9.4)
Running Speed & Agility	16.5 (4.26)	18.0 (3.14)	15.8 (5.28)	13.5 (2.52)
Strength	16.8 (4.49)	18.4 (3.79)	15.9 (5.00)	13.25 (2.87)
Strength and Agility SS	53.5 (9.41)	57.1 (6.97)	51.6 (11.24)	45.5 (5.26)
Total motor composite SS	48.7 (9.07)	50.75 (8.23)	47.5 (10.23)	44.25 (8.14)

Mean scores for Bruininks-Oseretsky Test of Motor Proficiency is 15 with an SD of 5 for individual items and 50 with an SD of 10 for standard scores. Data presented as mean (SD) or median (25^{th} – 75^{th} percentile). Abbreviations: BOT-2, Bruininks-Oseretsky Test of Motor Proficiency-2; TGA, Transposition of the Great Arteries; TOF, Tetralogy of Fallot; SVP, Single Ventricle Physiology; SS, Standard Score.

A total of 25 exercise tests were considered as maximal effort, as respiratory exchange ratio raised above 1.0 but heart rate at peak was inconclusive as it failed to raise above 180 beats per minute in the majority of the patients. See Table 4 for a full overview of the cardiopulmonary exercise test results. Minute ventilation/carbon dioxide production was elevated, as well as total ventilation in regard to workload at peak. Univariate analysis showed no baseline or clinical factors significantly related to peak exercise capacity.

Table 4 *Results cardiopulmonary exercise tests in children with a CHD (n=25)*

Age at test	6.43 (6.14 – 6.65)
Gender (male/female) (%)	16/9 (64/36)
Disease type (n (%))	
Fontan / Single Ventricle Physiology	2 (8)
Tetralogy of Fallot	10 (40)
Transposition of the Great Arteries	13 (52)
Height in cm / Z-score for age	118.37 (6.92) / -0.72 (1.24)
Weight in kg / Z-score for age	21.20 (18.75 – 22.9) / -0.42 (1.50)
Body Mass Index / Z-score for age	14.86 (14.28 – 16.02) / -0.0078 (1.20)
Heart rate at rest in beats/minute	88 (13)
Oxygen saturation at rest	99 (98 – 100)
Exercise capacity at anaerobic threshold in liter	0.60 (0.10) / 85.3 (14.8)
Heart rate at peak in beats/minute	167 (14)
Oxygen saturation at peak	99 (97 – 100)
Respiratory exchange ratio at peak	1.12 (0.07)
Exercise capacity at peak in liter	0.82 (0.13) / 79.1 (13.6)
Exercise capacity at peak in ml/kg/min	38.11 (5.39) / 83.3 (11.2)
Oxygen-pulse at peak	4.98 (0.92) / 97.1 (21.4)
ΔO2/Watt peak in ml/Watt	8.32 (1.84) / 84.4 (19.1)
Minute ventilation/carbon dioxide production slope at peak	33.14 (3.4) / 105.5 (10.4)
Workload at peak	61 (12.0) / 111.0 (25.0)
Workload per kg at peak	2.82 (0.40) / 94.4 (13.4)

Breathing frequency at peak	56 (11) / 95.8 (17.8)
Ventilation at peak in liter	33.3 (6.7)
Ventilation in regard to workload at peak (percentage)	108.0 (17.8)

Data presented as mean (SD) or median (25^{th}-75^{th} percentile) with percentage predicted (SD) if available unless otherwise stated. Abbreviations: cm, centimeter; kg, kilogram; ml/kg/min, milliliter per kilogram per minute; Δ, delta; ml/Watt, milliliter per Watt

DISCUSSION

This is the first study into the relationship between early motor development and exercise capacity during childhood in patients with (C)CHD. Current study indicate merely a weak and non-significant correlation between motor development at 3.5 years and peak exercise capacity between 6 and 7 years. A moderate significant correlation was found between motor development and exercise capacity both measured between 6 and 7 years. Motor development change over time was high, as two third of the patients improved or declined more than 1 Z-score. As a result, the correlation between both motor development assessments was weak and non-significant.

As stated above, no previous studies have been performed regarding the relation between early motor development and exercise capacity in children with CHD. Motor development and exercise capacity separately however, have been extensively described. Our current submitted review regarding motor development in children with a (C)CHD concluded that approximately a quarter of all included studies displayed abnormal mean motor developmental scores and children with the most severe type of CHD demonstrate the highest severity and prevalence levels of motor delay especially at a very young age (0-12 months) [49,50]. However, most studies merely test motor development at one point [51,52], failing to show changes over time. In some cases, only a percentage is given of patients with delayed motor development [53], resulting in even less insight into the motor development of this population. Exercise capacity has been repeatedly shown to be declined in children with CHD [54,55] and

also declines over age [56]. Nonetheless, only a weak association between early motor developmental outcomes and exercise capacity during childhood has been found in the current study. This questions whether early motor development outcomes can validly predict exercise capacity in this population. However, the current study also found a weak correlation between both total motor development scores, despite a strong correlation between the two different used motor developmental instruments inherent to age of assessment [57]. This indicates a unstable and highly variable motor development between 3.5 years and 6 to 7 years, as almost the same amount of patients improved, worsened or stayed at the same level of motor proficiency. These findings are in line with a previous study citing individual (neuro)development stability is only moderate at best [53]. This unstable and variable motor development in time could explain the found weak association and signifies the importance of individual clinical follow-up of these patients.

As we know that subtypes make a difference in motor development score, the results for motor development scores were described as extensive as possible. For instance, we see that 23.3% and 18.2% were at risk for or had delayed motor development at 3.5 years of age and between 6 and 7 years, respectively. In healthy children, only 5.5% is at risk for or have delayed motor development, indicating a much higher percentage in children with (C)CHD [58]. Perioperative low cardiac output [59,60], hypoxia [59] and duration of cardiac arrest during surgery [61,62] are all well-known causes for the impairments. We do see however, that our children with SVP are doing worse than the other subtypes which is in line with research showing single ventricular heart defects affect the brain more than biventricular heart defects [9,63]. Decreased cerebral perfusion as a result of reduced fetal cerebral oxygen consumption in children with SVP could affect cerebral development leading to a decreased motor development. Moreover, surgery in SVP patients is palliative leaving children with a non-optimal circulation, while

other lesions can be successfully repaired [58].

Our population scored ≈80% predicted on peak exercise capacity, which is considered the lower limit of normal [64]. Previous research shows that with increased severity, peak exercise capacity decreases [65]. In our study however, numbers were too small to identify differences between severity types. Nevertheless, the importance of (near) normal exercise capacity in children with CHD cannot be stressed enough as maximum exercise capacity has a strong correlation with quality of life in this population [66]. Furthermore, it is a strong predictor for mortality, morbidity and hospitalization [37–39,67] in adults with CHD. As peak exercise capacity is already at the lower limit of normal in our population, repeated measurement is of great importance and interventions into improving exercise capacity in children with CHD should be part of usual care.

As described in the results, heart rate at peak was inconclusive in determining whether the patients had reached maximal effort. Research shows that such chronotropic incompetence, the inability to raise heart rate appropriately during increased exercise, is commonly observed in children requiring cardiac surgery involving cardiopulmonary bypass [68], and particularly in most cyanotic disorders such as TGA and SVP [69,70]. Elevated minute ventilation/carbon dioxide production is frequently found in children with (C)CHD [65,71], indicating a reduced efficiency of gas exchange (e.g. ventilation/perfusion mismatch) [72]. As a result, ventilation increases to maximize carbon dioxide buffering leaving less energy available for muscle utilization. Consequently, these limiting factors might attribute to the reduced exercise capacity found in our population.

We did not find any baseline or clinical characteristics significantly related to peak exercise capacity at 6 to 7 years. However, a previous study in a large group of children with CHD (mean age 12.2), showed significant correlations between peak exercise capacity and number

of heart catheterizations and number of cardiac surgeries [73]. Another study in children with CHD (mean age 12.7) showed a significant correlation between disease severity and peak exercise capacity, meaning with increased severity peak exercise capacity declined [74]. We possibly have not found any related characteristics due to our small sample size or that these factors might develop their influence later on in childhood. However, to our knowledge there are no other studies into the relation between clinical characteristics and peak exercise capacity in younger children with CHD to compare with.

This study has some limitations to address. First of all, we did not reach our sample size goal of 46 which was not possible due to unforeseen circumstances (COVID-19 situation). Only 35 patients were included into the study of which there were only 20 patients that completed the motor development test at 3.5 years and had a valid maximal exercise test between 6 and 7 years. Consequently, due to lack of power the results of the current study should be interpreted with caution. Second, exercise tests were in almost all patients planned after the motor development test resulting in a total of 7 out of 32 exercise tests that were deemed no maximal effort as respiratory exchange ratio failed to raise above 1.0. Children with CHD should be capable of reaching such values at peak exercise [72], but almost 22% failed to reach this. Children might have been already tired from the first test, resulting in a reduced effort at the second test. However, as our patients sometimes have a long commute, planning these two tests sequentially has a preference over planning two separate appointments. Additionally, our study population might not be representative as the follow-up has merely a screening character. Children with multiple problems are in particular lost to follow-up as they are often extensively cared for elsewhere, making the current follow-up too burdensome or of little added value. Lastly, a regression analysis would have been better suitable to not only answer by what clinical factors peak exercise capacity is influenced but additionally to what extent.

However, this seemed invaluable with only 25 exercise tests available and consequently an univariate analysis was performed which unfortunately didn't yield any significant results.

In conclusion, we found no strong correlation between early motor development and peak exercise capacity. However, as motor development over time seems to be only moderately stable and peak exercise capacity is a strong predictor for hospitalization and mortality, a broad follow-up program including regular motor development tests and exercise tests should be part of usual care in children with (C)CHD in order to timely identify and intervene when individual problems occur. Future research should focus on exploring the association between early motor development and exercise capacity and identifying clinical characteristics directly related to exercise capacity in a large and preferably young cohort with diverse types of (C)CHD.

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Supplements

Table S1 Motor development change over time

Patient	Type of CHD	Z score MABC-2	Z-score BOT-2	Difference
CHD004	TGA	-1.0	0.20	+1.2
CHD005	TOF	0.0	-0.10	-0.1
CHD007	SVP	1.0	-0.40	-1.4
CHD008	TOF	-0.67	-0.50	+0.17
CHD009	TOF	0.33	-0.20	-0.53
CHD010	TGA	-0.33	0.90	+1.23
CHD011	TGA	-0.67	-0.50	+0.17
CHD012	SVP	0.33	-1.10	-1.43
CHD013	TGA	-2.00	0.40	+2.40

CHD014	TGA	-1.33	1.10	+2.43
CHD015	TGA	0.33	0.70	+0.37
CHD017	TOF	-1.00	0.30	+1.30
CHD018	TOF	0.00	0.00	0.00
CHD019	TGA	1.00	0.90	-0.10
CHD020	TOF	-0.33	-1.20	-0.87
CHD021	TGA	-0.67	-1.50	-0.83
CHD022	TGA	-0.67	1.40	+2.07
CHD023	TGA	0.67	0.50	-0.17
CHD024	TOF	-1.00	-0.90	+0.10
CHD025	SVP	0.00	0.50	+0.50
CHD026	TGA	-1.00	-0.60	+0.40
CHD027	TGA	0.67	-0.50	-1.17
CHD029	TGA	0.33	0.20	-0.13
CHD030	TOF	1.67	1.80	+0.13
CHD031	TGA	-1.00	-0.80	+0.20
CHD032	SVP	-0.67	-1.30	-0.63
CHD033	TOF	-0.67	-2.10	-1.43
CHD034	TOF	0.33	-1.50	-1.83

Abbreviations: CHD, Congenital Heart Defect; MABC-2, Movement Assessment Battery for Children-2; BOT-2, Bruininks-Oseretsky Test of Motor Proficiency-2; TGA, Transposition of the Great Arteries; TOF, Tetralogy of Fallot; SVP, Single Ventricle Physiology