Leg-focused high-weight resistance training improves ventricular stroke volume, exercise capacity and strength in young patients with a Fontan circulation

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Authors have no conflicts of interest to declare that are relevant to the content of this article.

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Ethical approval statement

The study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Erasmus MC (NL.70912.078.19).

Patient consent statement

All patients and parents signed informed consent.

Data availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Clinical trial registration:

The trial was registered at the international clinical trials registry platform of the world health organization (https://trialsearch.who.int/Trial2.aspx?TrialID=NL8181) as Trial NL8181.

Author contributions

LES, EMWJU, WAH, KD, LEB and the Rotterdam exercise team had the main role in the research protocol design. AH designed the magnetic resonance protocol, WAH acquired and analyzed CMR's. LES, LEB, LK and TP performed measurements. LES and TP did the statistical analyses. LES drafted the manuscript. All authors critically revised the manuscript and approved the final version. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Abstract

Introduction

Effective therapy to improve exercise capacity in Fontan patients is lacking. Leg-focused high-weight resistance training might augment the peripheral muscle pump and thereby improve exercise capacity.

Methods

This randomized semi-cross-over controlled trial investigated effects of a 12-week leg-focused high-weight resistance training plus high-protein diet, on (sub)maximal exercise capacity, cardiac function (assessed with cardiovascular magnetic resonance), muscle strength and quality of life in pediatric Fontan patients.

Results

Twenty-eight pediatric Fontan patients were included, 27 patients, (median age 12.9 [10.5–15.7]), successfully completed the program. Peak oxygen uptake (PeakVO$_2$) at baseline was reduced (33.3 ml/kg/min [27.1-37.4],73% [62–79] of predicted). After training PeakVO$_2$/kg and Peak workload improved significantly with +6.2 ml/kg/min [95%CI: 3.4–9.0](+18%) $p<0.001$ and +22 Watts [95%CI: 12–32](+18%) $p<0.001$ respectively, compared to the control period. Indexed single ventricle stroke volume increased significantly (43 ml/beat/m2 [40–49] versus 46 [41-53], p=0.014), as did inferior vena cava flow (21 ml/beat/m2 [18–24] versus 23 [20–28], p=0.015), while superior vena cava flow remained unchanged. Strength of all measured leg muscles increased significantly compared to the control period. Self-reported quality of life improved on the physical functioning and change in health domains of the child health questionnaire, parent-

reported quality of life improved on the bodily pain, general health perception, and change in health domains compared to the control period.

Conclusion

In a relatively large group of 27 older Fontan children, 12-weeks of leg-focused high-weight resistance training improved exercise capacity, stroke volume, (sub)maximal exercise capacity, muscle strength, and domains of quality of life.

Key Question

Is leg-focused high-weight resistance training an effective therapy to improve reduced exercise capacity in patients with a Fontan circulation ?

Key Finding

Twelve weeks of leg-focused high-weight resistance training in children with a Fontan circulation improved exercise capacity, single ventricular stroke volume, (sub)maximal exercise capacity, muscle strength, and physical domains of quality of life.

Take-home Message

Leg-focused high-weight resistance training results in improved exercise capacity, cardiac function, and quality of life patients with a Fontan circulation. Patients with a Fontan circulation should be motivated to perform lower limb strengthening exercises.

Introduction

The Fontan procedure consists of a series of operations performed in patients born with univentricular cardiac defects (1). Currently, approximately 70,000 patients with univentricular hearts are alive (2, 3). Improved health care has led to increased survival rates, causing the population of patients living with a Fontan circulation to grow rapidly (3). The estimated prevalence in 2030 is 79 Fontan patients per million people (4). Despite these advances, patients with a Fontan circulation still experience a decreased exercise capacity, which also deteriorates faster compared to healthy peers and is associated with a worse quality of life . (5, 6). Deterioration in exercise capacity has shown to be an important prognostic predictor of adverse events in patients with a Fontan circulation (7). The decreased exercise capacity is most likely caused by several factors, including the physiology of the Fontan circulation itself and decreased physical activity levels (8-10). In the Fontan procedure the systemic venous return is directly to the pulmonary arteries, without the support of a sub-pulmonary ventricle (1). During exercise Fontan patients fail to adequately increase venous return and thereby pulmonary blood flow, leading to a reduced ventricular preload and an inability to increase stroke volume, which has been referred to as the Fontan bottleneck (11-13).

Currently the only known non-invasive way to improve maximal exercise capacity in Fontan patients is exercise training. A recent systematic review published by our group showed that exercise is not only safe, but also leads to improvements in exercise capacity, cardiac function and quality of life in both children and adults with a Fontan circulation (8). Exercise types mainly investigated were aerobic training or a combination of aerobic and low weight resistance training, resulting in an improved exercise capacity in approximately 60% of the studies (8).

Several studies sought to improve exercise capacity in Fontan patients using inspiratory muscle training. This approach has not been successful yet. (8, 14) A study by Hjortdal et al. demonstrated that a way to attenuate the Fontan bottleneck during exercise in Fontan patients might be by contraction of the leg muscles, also called the peripheral muscle pump (12). This was further supported by a small study (n=6) published by Cordina et al., currently the only study investigating effects of high-weight resistance training in patients with a Fontan circulation (15). The current study aims to investigate the effects and safety of leg-focused high-weight resistance training, supported by a high-protein diet, on (sub) maximal exercise capacity, cardiac function, muscle strength and quality of life in (pediatric) Fontan patients.

Methods

This trial was a prospective randomized semi-cross-over controlled trial investigating 12-weeks of leg-focused high-weight resistance training, supported by a high-protein diet in children with a Fontan circulation. This trial was conducted between December 2020 and July 2022 at the Erasmus MC – Sophia children's hospital, department of pediatric cardiology, the Netherlands. The study was performed in accordance with the Declaration of Helsinki. It was approved by the local Ethics Committee of Erasmus MC (NL.70912.078.19) and registered at www.trialregister.nl as Trial NL8181. This study was part of a larger study, investigating exercise in children with various chronic diseases. A detailed protocol of this study was published before (16).

Participants

Children with univentricular heart defects who had a completed series of interventions resulting in the Fontan circulation, aged 6-18 years, were eligible for enrollment. Physical inability to perform a cardiopulmonary exercise test (CPET), participation in other exercise training programs, and contra-indications for exercise (ventricular outflow obstruction gradient of > 60 mmHg and / or arrhythmias) were exclusion criteria. All patients were recruited at the outpatient clinic of the Erasmus MC - Sophia children's hospital, Rotterdam, the Netherlands. Informed consent was obtained from all participants and/or parents before enrollment.

Study design and intervention

Figure 1 shows the study design, visits, and measurements. Randomization was performed in blocks of 4 or 6 using Castor (Clinical electronic Data Capture)(17). All children were randomized to group A (start exercise) or group B (start control period, duration 6 weeks). Group A started the intervention immediately after the first assessment, group B started after a period of 6 weeks during which they received routine care without any treatment/ physical activity changes (yielding a 2:1 ratio of intervention versus control measurements). Each study visit consisted of two assessment days with at least 3 days and maximally 7 days in between during which patients continued normal daily life. The tailored lifestyle intervention was designed as previously described in our trial design paper (16). The tailored individual physical training program lasted 12 weeks, and consisted of 3 supervised training sessions per week (training, supervision and motivation was performed by a physiotherapist close to participant's home) lasting around 45 minutes each. The training program started with 10 minutes of walking on a treadmill with maximal incline, rowing or cross trainer exercise, where after children performed progressive overload resistance training focused on the leg-muscles. Each exercise was performed in 3 sets of 6-8 repetitions. Whenever a child could perform 3 times 8 repetitions, more weight was added to the exercise. Exercises included: Squats, (single) standing/seated calf raises, hip trusts, (knee rise) step-ups, jump ups, leg press, leg abduction and leg adduction, donkey kicks, mountain climbers and the back bridge. To compensate for missed training sessions, we prolonged the intervention by one week if children missed more than 1 training session in a week. The full training program can be found in supplemental table 1. As it has been shownrepeatedly that an increased protein intake positively impacts muscle gain during resistance training, our dietitian prescribed a high-protein diet of 2 gram/kg per day (18). Children also received a recommended caloric intake per day,total energy expenditure (calculated using the Schofield formula and based on measured rest energy expenditure (REE) and corrected for weight) and a brochure regarding a healthy diet in children(designed by the 'Voedingscentrum', the Dutch government supported nutritional center) (19). LES visited all first training sessions and a training (either live or via video connection) of each patient every 2 weeks, to monitor uniform execution of the training program. During the intervention, LES telephoned patients weekly to monitor safety, side effects and assure compliance for both the training and dietary advice (by complimenting and motivating the children).

Outcome measurements

The primary study outcome was change in peak oxygen uptake (peak VO_2/kg), the golden standard for cardiorespiratory fitness. Secondary outcomes were submaximal endurance, cardiac function (measured using cardiovascular magnetic resonance (CMR) and echocardiography), muscle strength, quality of life, fatigue, fears of exercise, energy balance and body composition. A detailed description of all measurements and protocols used is provided in the previously published Exercise Study protocol (16).

Cardiorespiratory fitness

Maximal exercise capacity and endurance were assessed by maximal CPET, submaximal CPET, and 6-minute walking test (6MWT). All patients underwent the maximal CPET (ramp protocol), and submaximal CPET on the same electrically braked bicycle ergometer: Jaeger ER9000 (Viasys Healthcare, Hoechberg, Germany). The maximal CPET started with 1 minute (min) of unloaded cycling with a rate of 60–80 repetitions per minute, where after exercise intensity was increased progressively until exhaustion (Ramp protocol). The rate of increase was chosen considering the patient's functional capacities (between 10 Watt/min and 25 Watt/min). Patients continued until exhaustion. PeakVO_2 was the highest mean value during 8 breaths. The submaximal CPET started with 3 min of unloaded cycling, followed by 6 min of cycling with an exercise intensity set on half of the previously reached maximum workload during the maximal CPET, and ended with a 3-minute recovery phase. During both maximal and submaximal CPET, respiratory parameters and heart rhythm were continuously measured using respectively breath by breath analyses: Oxycon Champion System (Viasys Healthcare, Conshohocken, United States) and 12 lead ECG. Blood pressure was measured every 2 minutes. Exercise tests with a peak respiratory exchange rate (RER) ≥ 1.00 and Heart rate reserve (HRR) <20, were considered maximal. PeakVO_2/kg was compared to PeakVO_2/kg outcomes of a large cohort of healthy Dutch children (based on age and sex) published previously.(20) The 6MWT was performed in accordance with the American Thoracic Society guidelines, however due to a lack of space, the course was 8 meters of length instead of 30 meters.

Cardiac function

CMR was performed on a 1.5 T Signa Explorer MRI scanner from GE healthcare (Milwaukee, Wisconsin, USA). A multi-phase, multi-slice volumetric data set was acquired using a fast 2D cine scan using balanced steady-state free precession (slice thickness 8 mm, no interslice gap, flip angle 45 degrees, the field of view dependent on body size and varied between 280 mm to 370 mm, phase of view 0.75, matrix size 224 x 192, repetition time 3.5 ms, echo time 1.5 ms, reconstructed in 30 phases/cycle, mean in-plane resolution approximately 1.5 mm^2)(21). ECG gated flow images were acquired during continuous breathing to eliminate respiratory effects using a 2D phase contrast sequence (slice thickness of 7 mm, flip angle 18 degrees, the field of view dependent on body size and varied between 250 to 320 mm, phase field of view was between 0.8 - 1.0, matrix size 192 x 160, echo time 3.2 (between 2.9-3.4), rep time 5.7 (between 5.4-6.0), views per segment 4, resulting in a temporal resolution of approximately 22 ms, unidirectional velocity encoding of 60 - 180 cm/s, reconstructed in 30 phases/cycle, mean in-plane resolution 1.4 mm^2). Flow was measured in the inferior vena cava (IVC), superior vena cava (SVC), right and left pulmonary artery and aorta. Analyses was performed with the software packages QMASS and QFLOW (Medis Medical Imaging Systems, The Netherlands) by an experienced pediatric cardiologist (WAH), who was blinded to the randomization and training state of the patients. Afterload was estimated as mean arterial pressure / cardiac index. Mean arterial pressure was estimated as diastolic pressure + 1/3*(systolic pressure – diastolic pressure). Cardiac index was estimated by stroke volume (SV)* heartrate (HR)/ body surface area (BSA). Echocardiograms were performed by echocardiography technicians, following the recommendations of the American Society of Echocardiography using the Philips EPIC7C (Andover, MA, USA) and using a Vivid E9 (General Electric Vingmed Ultrasound, Horten, Norway) ultrasound systems (42). Images were analyzed using Intellispace Cardiovascular software (Philips, Best, The Netherlands) by experienced echocardiography technicians. NT-pro-BNP levels, taken from a peripheral vein before any other tests were performed, were measured before and after the control period and exercise period and analyzed in the clinical laboratory of the Erasmus MC - Sophia's children hospital (cobas 8000 e801, Roche Diagnostics, Mannheim, Germany). Adverse events were defined as death, cardiac reinterventions, unscheduled hospitalization or outpatient visits for cardiac reasons, heart failure and arrhythmias.

Quality of life

The validated child health questionnaire (CHQ) child form (CHQ-CF45 including 45 items and 11 domains) and parent form (PF) (CHQ-PF28 including 28 items and 13 domains) were used to assess health-related quality of life before and after the intervention. (22) Baseline outcomes were compared to the healthy population. Data was compared to previously published data in healthy Dutch children (n=737) and their parents (n=4538) (22-24)

Muscle strength and core stability

All muscle strength measurements (shoulder abductors, elbow flexors and -extensors, hip flexors, hip abductors and -adductors, knee extensors and -flexors and hand-grip squeezing strength) were performed in a standardized manner by the same trained investigator (LES) using the citec hand-held dynamometer (CITEC HHD CT3002/30, CIT Technics, Haren, Netherlands). As part of the standard whole body strength assessment we measured core stability using time in balance for each of the following four core stability exercises: plank, back bridge, left side bridge, and right side bridge.

Physical activity levels

Parents (or children if they came alone) were asked about the amount of time spent on physical activity (hours and type of sport participation at school, and outside of school) a week using a structured questionnaire. Subsequently, physical activity levels were measured with a validated waist-worn Actigraph GT3X+ accelerometer for 2 weekdays and 1 weekend day (ActiGraph, Pensacol, USA).

Sample size calculation and statistical analysis

The power calculation for this study was based on the primary study outcome of change in peak VO_2 after the physical training program. In a previous study, untrained children with a Fontan circulation had a mean PeakVO_2 of 27 ml/kg/min (25). Twenty-one patients were needed in order to detect an increase in PeakVO_2 of at least 5%, (which we use as the clinically relevant increase in clinical setting in our hospital), with a power of 80% and an alpha of 0.05 based on a standard deviation of 2.19 VO_2/Kg. (26) Anticipating a dropout rate of 30-40%, 28 patients with a Fontan circulation were included in this study. Data were collected in Castor (Clinical electronic Data Capture)(17), all analyses were performed using IBM SPSS Statistics 25.0 (IBM Corp, Armonk, NY). Patient characteristics were described using median [IQR] or frequencies.

Baseline characteristics between groups were compared with the Mann-Whitney U and Chi-squared test for proportions. All data was analyzed as non-parametric due to the small sample size. Difference between baseline quality of life domains and healthy population were analyzed using the Wilcoxon one sample test. Differences over the exercise period and control period were analyzed using the Wilcoxon signed ranks test and McNemar-bowker test for proportions. A generalized estimations equations approach model was used to compare change over the control to the exercise period (described as the effect size including 95% confidence interval and corresponding P-value) account for the correlation of the repeated measurements in the control/active group. The working correlation matrix was set as unstructured. The significance level was determined at $P < 0.05$.

Results

Patient characteristics

In total 40 patients were contacted to participate in the study. Twenty-eight patients and their parents consented to participation. Reasons not to participate were; too busy with school obligations (n=6), parents were unable to bring the child to the hospital/ physical therapist (n=3), private circumstances (n=1), already playing sports >3 times a week (n=1), and one patient was scheduled for an operation. The median age of the participating patients was 12.9 [10.5 – 15.7] years, 37% was female. All patients were operated using the intra-atrial later tunnel technique for the total cavo-pulmonary connection. Patient characteristics can be found in table 1, both participant groups were similar at baseline. In total, 27 patients successfully completed the exercise intervention. One patient dropped-out after the first training session, as parents were unable to bring him to the training sessions. Compliance was high, with a median training session attendance of 33 [32 – 34] out of 36 session. All children continued to improve in amount of weight used during exercises throughout the training weeks, none deteriorated. Post-exercise measurements were performed 3 weeks early in one child, as parents were also unable to bring her to the training sessions from week 9 onward. The youngest child included in our study participated in 2 training sessions a week from week 6 onward, as the training frequency was too high for her.

Cardiorespiratory fitness

All patients performed a maximal CPET before and after the intervention (RER>1.0), data in table 2. The primary outcome, PeakVO$_2$/kg increased significantly after 12 weeks of training from 33.3 ml/kg/min [27.1 – 37.4] to 35.5 ml/kg/min [29.7 – 38.6], P<0.001 compared to controls (table 2). PeakVO$_2$, Wattmax and Wattmax/kg also improved significantly compared to the control period (respectively +234 ml/min [137 – 331], +22 Watt [12 – 32], +0.3 Watt/kg [0.2 – 0.5] P<0.001 for all)-. PeakVO$_2$ and workload decreased over the control period. Maximal and average heartrate, measured during the submaximal CPET, decreased significantly compared to the control period (respectively -8 bpm [-15 – 4], p= 0.042 and -8 bpm [-14 - -1], p=0.019). Walked distance on the 6MWT increased significantly after training compared to controls.

Cardiac function

Indexed stroke volume (SVi), aortic flow and IVC flow measured by CMR increased significantly after 12 weeks of training (table 3). Flow increased to the left pulmonary artery and aorta, but not to the right pulmonary artery. Superior vena cava (SVC) flow remained unchanged. Estimated afterload decreased significantly (from 29 mmHg/L/min/m^2 [21 – 33] to 25 mmHg/L/min/m^2 [21 – 28], p=0.045). Indexed ventricular mass, end diastolic volume and end systolic volume, did not change significantly. Mass/ end diastolic volume ratio also remained unchanged. Cardiac function was also evaluated using echocardiography. Maximum peak flow velocities in the aorta and across the dominant atrioventricular valve (Doppler E and A and E/A ratio) did not change significantly after training (table 3). Subjective ventricular function and presence and grade of aortic and dominant atrioventricular valve insufficiency did not change significantly.

Quality of life

Child reported quality of life was decreased compared to healthy children for the domains of physical functioning, mental health and general health perceptions, whereas Fontan children scored higher on family activities (supplemental table 2). Parents reported a decreased quality of life on 6 domains, and also scored higher on the family activities domain compared to parents of healthy children. After training, child reported quality of life improved on the domains of physical functioning and change in health compared to the control period (supplemental table 2). Parental reported quality of life improved significantly on 3 domains compared to the control period; bodily pain, general health perception and change in health.

Muscle strength and core stability

Muscle strength of 7 out of 9 measured muscle groups (shoulder abductors, elbow flexors and extensors, hip flexors, hip adductors, hip abductors, knee flexors and extensors) increased significantly (\table 4). Core stability improved significantly for the plank and back bridge compared to the control period.

Physical activity levels

In total, 8 out of 28 children participated in sport activities (besides school related physical exercise) prior to the study. Median percentage of time spent in moderate-to-very-vigorous activity measured with the Actigraph did not change significantly after the intervention (supplemental table 3). After 12 weeks of exercise, 18 children continued to participate in some form of sports activities, of which 12continued physical therapy for at least once a week.

Safety

Median NT-pro BNP levels were within normal limits and did not change significantly after training (13 pmol/L [6 – 16] vs 13 pmol/L [8 – 18], p=0.177). No (cardiac) adverse events, including arrhythmias, were observed during the trial or measurement days. Shortly after the intervention, a low albumin was found in a patient during a clinically indicated blood draw. Eventually, the child was diagnosed with protein losing enteropathy. We are uncertain when the protein losing enteropathy started, as both parents and the child did not report on any symptoms during the weekly phone check-ups during the study and albumin was not measured before the intervention.

Discussion

This RCT is the first to investigate the effects of leg-focused high-weight resistance training in a relatively large group of teenage children with a Fontan circulation. The 12-week training intervention (supported by high-protein diet) improved exercise capacity, cardiorespiratory fitness, indexed ventricular stroke volume, muscle strength, core-stability and physical quality of life.

Cardiorespiratory fitness

As expected, at baseline, patients had a decreased exercise capacity compared to healthy peers (median 33.3 ml/kg/min, 73.2% of predicted). $PeakVO_2$/kg was comparable to previously published normal values in Fontan patients and a cross-sectional study in our own center, indicating that participants in our study were representative for the Fontan population, and inclusion bias towards (un)fitter patients was unlikely (21, 27). After the tailored intervention, exercise capacity measured by $PeakVO_2$ improved significantly with +6.2 ml/kg/min (+18%), $p<0.001$ compared to controls. This is higher than the average improvement of +1.7 ml/kg/min (+6%) found in a systematic review including 264 Fontan patients who participated in different kinds of exercise interventions (8). A small study (n=6) investigating effects of high-weight resistance training focusing on the lower limbs in adults with a Fontan circulation also found a significant improvement in $PeakVO_2$ (+7%) (15). Avitabile et al. recently also conducted a training program focused on the lower-limbs in Fontan patients and did not show an increase in exercise capacity. However, in the study by Avitabile resistance was kept at 60% of pretraining maximum, which is not high-weight resistance training (28). In the current study, peak work load increased significantly, most likely caused by the large increase in strength of all (leg) muscle groups assessed. Over the control period children decreased significantly on PeakVO_2 and peak workload, possibly indicating decreased physical activity during the 6 week control period. However this was not indicated by both Actigraph measurements and the structured questionnaire. Note that peak RER values at start and end of the control period indicated comparable effort at CPETs. Heart rate changes over the control period were not significantly different from those in the exercise period. The distance walked during the 6MWT increased and average and maximal heartrate during submaximal CPET decreased significantly following training, showing an improved (submaximal) endurance. This is an important improvement. Athough maximal exercise capacity is widely used as the golden standard for physical fitness, submaximal exercise capacity is more representative of physical functioning during daily life activities, and improvements in submaximal outcomes might therefore be more relevant to patients. Two previous studies which looked at the effects of training on walked distance in Fontan patients after a training intervention also found a significant improvement. (29, 30)

Cardiac function

In the healthy population aerobic training leads to physiological cardiac remodeling including eccentric hypertrophy (balanced increase of chamber and wall dimensions), and improved contractility and diastolic filling. (31, 32) Although this has not been researched extensively, various studies, including the 'Morganroth hypothesis', have suggested that resistance training might lead to concentric hypertrophy. (33) A large meta-analysis by Utomi et al. in male athletes found no training specific pattern of concentric hypertrophy in resistance athletes, but rather an eccentric hypertrophy, although present to a lesser extent compared to aerobic athletes. (32) Cardiac enhancing effects of resistance training, with improvements in both systolic and diastolic function, have been demonstrated in adults with diastolic dysfunction and cardiac failure. (13, 34) Augmentation of the peripheral muscle pump, the largest contributor to venous return into the IVC during exercise in Fontan patients, has repeatedly been suggested as adjuvant therapy in Fontan patients, as impaired single ventricular filling forms the main problem during exercise. (11-13, 35, 36) With high-weight leg-focused resistance training supported by a high-protein diet, we tried to enlarge the peripheral muscle pump. After 12 weeks of training, indexed IVC flow increased significantly, possibly leading to the increased pulmonary blood flow in the left pulmonary artery and thereby improved stroke volume and aortic flow. SVC flow did not change in our study, which strengthens our impression that the increase in stroke volume and $PeakVO_2$ might be attributable to the augmentation of the peripheral muscle pump of the lower body. Only flow in the left pulmonary artery increased significantly, which is most likely explained by the fact that SVC flow in Fontan patients predominantly contributes to the right pulmonary artery, while almost 70% of IVC blood flows towards the left pulmonary artery. (12, 37) Surprisingly, we did not note changes in ventricular volumes, which might be due to a lack in power or poor repeatability of CMR in complex congenital hearts. Another explanation of improved stroke volume could be that the resistance training decreased the peripheral vascular resistance, leading to an improved afterload and thereby increased stroke volume and aortic flow in Fontan patients. In healthy subjects, resistance training has been shown to decrease blood pressure, increase peripheral flow and improve endothelial function. (38) In our study, estimated afterload decreased significantly, mainly caused by decreases in diastolic blood pressure and increased stroke volume. Importantly, no signs of (pathological) cardiac remodeling or hypertrophy were seen in the Fontan patients, as mass and mass/ EDVi ratio remained unchanged after the intervention. (39) A meta-analysis investigating resistance training in acquired heart failure patients also found no detrimental effects on cardiac structures. (13) Only two previous studies measured cardiac function using CMR in Fontan patients before and after a training intervention. An RCT, executed in our center, investigating aerobic training using the same CMR protocol in children with a Fontan circulation, did not find any changes in cardiac function or structure after training. (40) A study investigating the effects of inspiratory muscle training in Fontan patients found an increased cardiac output at rest but not during stress CMR. (15, 41) The only previous study investigating high-weight resistance training in Fontan patients measured a significant decrease in IVC flow, aortic flow and stroke volume following a 12-month detrain period (n=4). (15)

Quality of life

A meta-analysis investigating quality of life in Fontan patients, showed that patients (and their parents) report a decreased quality of life across all domains compared to healthy peers. (42) In our cohort, children (and parents) also scored lower on several domains, with the lowest scores on the general health perception and physical functioning domains. After training, child-reported quality of life improved on physical functioning (to the level of healthy children) and change in health compared to the control period. This was in accordance with the feedback of the children, as they reported to feel fitter and healthier. Parents reported quality of life improvements on 3 domains compared to the control period. Most previously published training intervention studies also reported positive outcomes on quality of life after exercise interventions. (8)

Physical activity levels

In our cohort, only 8 out of 28 patients participated in some form of sports activities besides school related physical activity, this was below the recommended Dutch guidelines of >1 hour a day of moderate to vigorous physical activity and muscle strengthening activities for at least three times a week. (43) Previous studies have also reported decreased physical activity levels in children and adolescents with a Fontan circulation. (44, 45) After the 12 week intervention, ten children in the current cohort who did not exercise before, continued to participate in some form of sport. Based on available Actigraph results, this did not result in increased activity levels, as measured moderate to vigorous physical activity time did not increase after the intervention. Three previous studies investigating effects of a training intervention on amount of time spend in physical activity all did not find an increase in moderate to vigorous physical activity directly after training. (46-48) However, the only study with a long-term follow-up showed an increase in physical activity with 36 ± 31 min/week, one year after the training intervention (with no additional interventions). (48)

Strengths and Limitations

Our study has several strengths and limitations. This RCT is the first to investigate the effects of leg-focused high-weight resistance training supported by high-protein diet in a large group of children with a Fontan circulation on a broad range of outcomes. A weakness of our study is the small control group, existing of 14 patients, the study should be validated in a larger cohort. Also, cardiac imaging using CMR was not performed before and after the control period. However, in a study published by our group in 2015 with comparable CMR protocol, no changes in any parameters were seen over a 12 week control period in a group of 17 Fontan children. (40) Stress CMR was not performed in the current study due to the time-consuming nature of the procedure in an already long study protocol, in part caused by extensive high temporal resolution flow measurement during free-breathing. Except for CMR analyses, researchers in the study could not be blinded during measurements due to the nature of the study. By following specific guidelines on encouragement during for example the 6MWT, this bias was minimized. Our CPET system does not provide OEUS or VE/VCO2 data, these parameters are particularly of added value when patients are unable to reach PeakVO$_2$, however in this study all patients reached RER>1.0. (49) As our study partly took place during the COVID-pandemic, six children developed COVID-19 right before or during the 12 week intervention. To compensate for missed training sessions, we prolonged the intervention by one week if children missed more than 1 training session in a week.

Safety, patients experience and recommendations

Overall the 12-week high weight resistance training was very well received, as reflected by the high training adherence and increases in quality of life. Most children (and their parents on their children) reported to feel fitter and stronger after the intervention, and several children indicated that they liked this form of training in contrast to other sport activities where they would often feel inferior compared to (healthy) peers. We did notice that the training frequency of 3 times a week was perceived as high, mainly in the younger children. A lower training frequency and more varied program might be more suitable for the long-term. Besides positive effects on endurance, cardiac function and quality of life, the amount of children who continued some form of sports activities after participating in the study more than doubled, indicating that the intervention resulted in positive effects on their lifestyle. Currently, (high intensity) strength training is not recommended in patients with severe congenital cardiac diseases, as fears regarding adverse effects on ventricular function and structure exist. (50) However, the last two decades resistance training has emerged in exercise recommendations in adults with acquired cardiovascular disease, including cardiac failure. (13) As in our study, a meta-analysis investigating resistance training effects in patients with acquired cardiac failure (including over 100 patients) found no serious cardiovascular events or remodeling. However, long-term follow-up (>1-2 years) is still lacking. (13) Not only has exercise (and especially strength) training not been associated with adverse effects in Fontan patients, other treatment forms, including medication, are currently not as effective to improve (> 5% increase) in PeakVO$_2$ in Fontan patients. (51, 52) The FUEL trial, investigating udenafil in 400 Fontan patients, did not demonstrate a significant increase in maximal exercise paramaters. This trial did show improvements in submaximal exercise, including multiple measures of exercise performance at the ventilatory anaerobic threshold. (53)

When considering all results, we think resistance training, or other fitting sports boosting the peripheral muscle pump, should be actively encouraged in patients with a Fontan circulation.

Of note, this is a low cost approach, available throughout the world, improving how patients function and feel.

Conclusion

This study is the first to investigate leg-focused high-weight resistance training supported by high-protein diet in a relatively large group of older children with a Fontan circulation. This approach resulted in augmentation of leg strength, increased ventricular stroke volume and (sub)maximal exercise capacity, and improved physical quality of life in children with a Fontan circulation. Patients with a Fontan circulation should be motivated to perform lower limb strengthening exercise.

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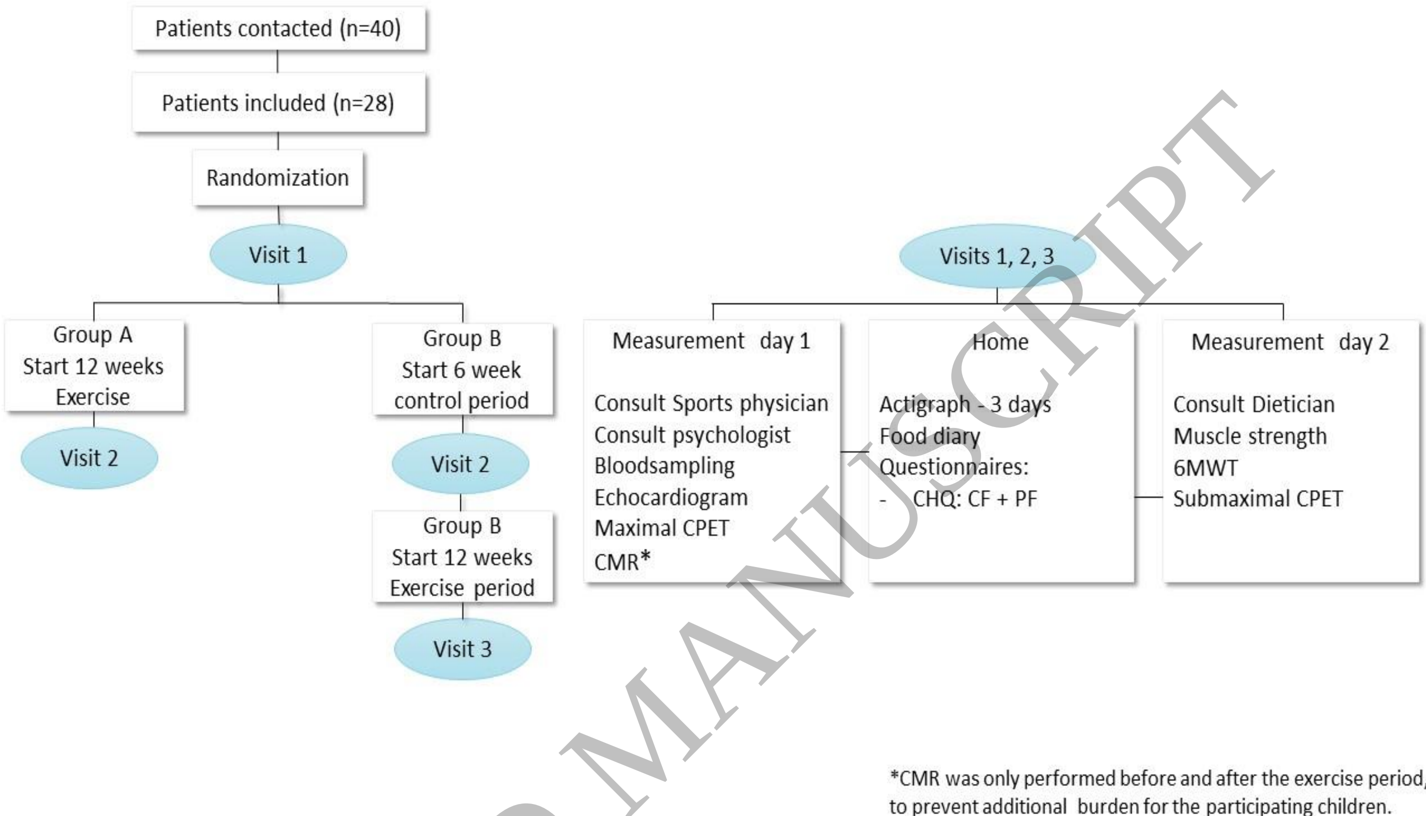
Figure 1: Study design and visits and measurment assessments.



Left figure: shows the study design. Patients were randomised into 2 groups, group A started with 12 weeks of exercise, group B started with a 6 week control period, where after they also started 12 weeks of exercise. Visits consisted of 2 measurement days with minimum 2 an maximum 7 days in-between. Visit 2 was used as the before exercise value for group B, whereas this was visit 1 for group A. Right figure: shows the measurements performed each visit in detail. Abbreviations: CPET (cardiopulmonary exercise test), CF (child form), PF (parents form), CHQ (child health questionnaire), 6MWT (six minute walking test), CMR (magnetic resonance).

Table 1: Patient Characteristics

	Study population (n=27)	Group A (n=13)	Group B (n=14)	P-values
Female, n (%)	10 (37)	4 (31)	6 (43)	0.516
Age, years	12.9 [10.5 – 15.7]	12.8 [10.5 – 15.7]	12.9 [10.5 – 15.6]	0.792
Age at Fontan completion, years	2.8 [2.3 – 3.8]	2.7 [2.1 – 3.9]	3.1 [2.6 – 3.6]	0.413
Body mass index, kg/m²	17.8 [16.8 – 19.2]	17.2 [16.8 – 18.7]	18.0 [17.3 – 19.2]	0.881
Diagnosis, n				
Double inlet left ventricle	4	3	1	0.651
Pulmonary atresia	6	2	4	
Tricuspid atresia	3	2	1	
Hypoplastic left heart syndrome	8	3	5	
Double outlet right ventricle	6	3	3	
Dominant ventricle, n				
Left	10	4	6	0.707
Right	14	6	8	
Other	3	2	1	
Medication during study, n				
Vitamin K antagonist	8	3	5	0.822
Platelet inhibitor	19	10	9	
ACE inhibitor	2	2	0	
Beta-blocker	2	1	1	
Diuretic	0	0	0	

Data is presented as median [IQR], number (n)/ percentage (%). Difference between group A and B was calculated using the MannWhitney U or Chi-square test for proportions. Abbreviations: BMI (Body Weight Index), IVS (intact ventricular septum), VSD (ventricular septal defect), TA (Tricuspid atresia), ACE (Angiotensin-converting enzyme).

Table 2: Exercise capacity

	Exercise Period (n=27)			**Control Period (n=14)**				
	Before	After	P-values	Before	After	P-values	Effects size vs control period [95% CI]	P-value differenc exercise vs control period
Maximal CPET								
VO_{2PEAK} (mL·min^{-1})	1385 [1092 – 1754]	1513 [1247 – 1984]	**<0.001***	1416 [1122 – 1723]	1280 [1071 – 1713]	**0.020***	234 [137 – 331]	**<0.001***
VO_{2PEAK} (ml·kg·min^{-1})	33.3 [27.1 – 37.4]	35.5 [29.7 – 38.6]	**0.004***	35.2 [29.7 – 43.2]	33.3 [26 – 36.5]	**0.005***	6.2 [3.4 – 9]	**<0.001***
Percentage predicted $VO_{2PEAK/kg}$ (%)	73.2 [62.4 – 78.6]	76.8 [67.7 – 84.35]	**0.007***	80 [70.3 – 88.0]	68 [62.7 – 74.4]	**0.005***	12.5 [5.9 – 13.8]	**<0.001***
$Watt_{MAX}$ (Watts)	122 [79 – 141]	129 [95 – 165]	**<0.001***	96.5 [87.3 – 154.5]	88 [74.5 – 144.3]	**0.014***	22 [12 – 32]	**<0.001***
$Watt_{MAX}$ (Watts/kg)	2.6 [2.2 – 2.9]	2.8 [2.3 – 3.2]	**0.005***	2.8 [2.2 – 3.1]	2.6 [2.0 – 2.8]	**0.001***	0.3 [0.2 – 0.5]	**<0.001***
HR_{PEAK} (beats·min^{-1})	160 [148 – 171]	163 [149 – 179]	0.629	166 [151.3 – 181]	151 [136.8 – 175.5]	**0.006***	6 [-3 – 15]	0.187
RER_{Peak}	1.17 [1.09 – 1.23]	1.12 [1.05 – 1.15]	**0.015***	1.13 [1.02 – 1.20]	1.14 [1.1 – 1.2]	**0.036***	-0.1 [-0.2 – 0]	**<0.001***
$VO_{2\ at\ VT2}$ (mL·min^{-1})[1]	1179 [932 – 1511]	1176 [1014 – 1554]	0.903	1142 [987 – 1378]	997 [852 – 1346]	0.116	91 [-57 – 240]	0.228
O_2 – pulse at VO_{2PEAK}	9.4 [8.1 – 12.6]	9.9 [8.6 – 12.3]	0.071	9.3 [7.0 – 11.1]	8.9 [6.7 – 12.7]	0.783	1 [-0.1 – 2]	0.074
Systolic BP rest (mmHg)	117 [100 – 132]	114 [102 – 124]	0.419	113 [104 -127]	117 [101 – 129]	0.826	-5 [-20 -10]	0.513
Diastolic BP rest (mmHg)	70 [60 – 80]	68 [54 – 76]	0.082	64 [56 – 79]	69 [54 – 78]	0.861	-10 [-22 -3]	0.118
Submaximal CPET								
HR average (beats·min^{-1})	130 [115 – 140]	123 [108 – 137]	**0.045***	126 [112 – 144]	127 [114 – 143]	0.937	-8 [-15 – 4]	**0.042***
HR_{PEAK} (beats·min^{-1})	145 [124 – 151]	132 [120 – 149]	**0.034***	136 [120 – 162]	136 [123 – 157]	0.944	-8 [-14 – -1]	**0.019***
6MWT								
Walked distance (m)	496 [448 – 520]	524 [482 – 584]	**0.006***	491 [430 – 523]	494 [460 – 507]	0.402	28 [4 – 51]	**0.021***

Data is presented as median [IQR]. Differences over the exercise period and control period were analyzed using the Wilcoxon signed ranks test and McNemar-bowker test for proportions. A generalized equations approach model was used to compare change over the control to the exercise period (described as the effect size including 95% confidence interval and matching p-value). Abbreviations: CI (confidence interval), VO2 (oxygen uptake), ml (millilitres), min (minutes), kg (kilogram), Watt (wattage), Max (maximal), HR (heartrate), VT2 (ventilatory anaerobic threshold), 6MWT (6 minute walking test), m (meters), Bp (bloodpressure). 1: n=22, in 5 patients VAT before or after exercise could not be determined with certainty.

Table 3: Cardiac Function measured using CMR and echocardiograms

	Before	After	P-values
Cardiovascular magnetic resonance (n=25)			
Body surface area (m^2)	1.35 [1.16 – 1.60]	1.38 [1.18 – 1.64]	**<0.001***
Heart rate(beats per minute)	74 [62 - 82]	72 [63 – 83]	0.273
Single ventricular mass indexed (grams/m^2)	57 [40 – 77]	62 [50 – 77]	0.236
Mass/EDV ratio (gram/ml)[3]	0.66 [0.57 – 0.84]	0.73 [0.58 – 0.85]	0.408
SVi (ml/m^2)	42.8 [39.8 – 49]	46.0 [40.6 – 52.9]	**0.014***
Cardiac output indexed (L/min/ m^2)	3.3 [2.9 -3.5]	3.5 [2.9 – 3.8]	0.058
EF (%)	53 [48 – 63]	56 [51 – 62]	0.457
EDVi (ml/m^2)	81.5 [73.0 – 92.6]	81.4 [75.5 – 90.8]	0.619
ESVi (ml/m^2)	40.4 [29.9 – 44.2]	38.3 [29.4 – 46.9]	0.989
Flow measurements[1]			
Aortic flow (ml/beat/ m^2) (n=24)	40 [34 – 45]	41 [37 – 51]	**0.007***
Left pulmonary artery flow (ml/beat/m^2) (n=24)	11 [9 - 15]	13 [10 – 16]	**0.046***
Right pulmonary artery flow (ml/beat/m^2) (n=24)	12 [10 – 16]	15 [10 – 19]	0.211
SVC flow (ml/beat/ m^2) (n=20)	11 [10 – 15]	10 [9 – 13]	0.102
IVC flow (ml/beat/ m^2) (n=24)	21 [18 – 24]	23 [20 – 28]	**0.044***
Echocardiography (n=25)			
Dominant AV-Valve peak E (cm/s)	76 [66 – 87]	71 [63 – 82]	0.198
Dominant AV-Valve peak A (cm/s)	53 [43 – 62]	42 [38 – 49]	0.053
Dominant AV E/A ratio	1.5 [1.2 – 1.8]	1.3 [1.7 – 1.8]	0.277
Ascending aorta peak (cm/s)	102 [85 – 119]	110 [95 – 121]	0.424
Descending aorta peak (cm/s)	124 [114 – 180]	131 [115 – 173]	0.563
Systolic ventricular function (n)			
Good	15	17	0.500
Moderate	10	8	
Aortic insufficiency (n)[1]			
None / trivial	21	20	0.317
Mild	3	4	
AV insufficiency (n)			
None / trivial	8	11	0.223
Mild	13	10	
Moderate	4	4	

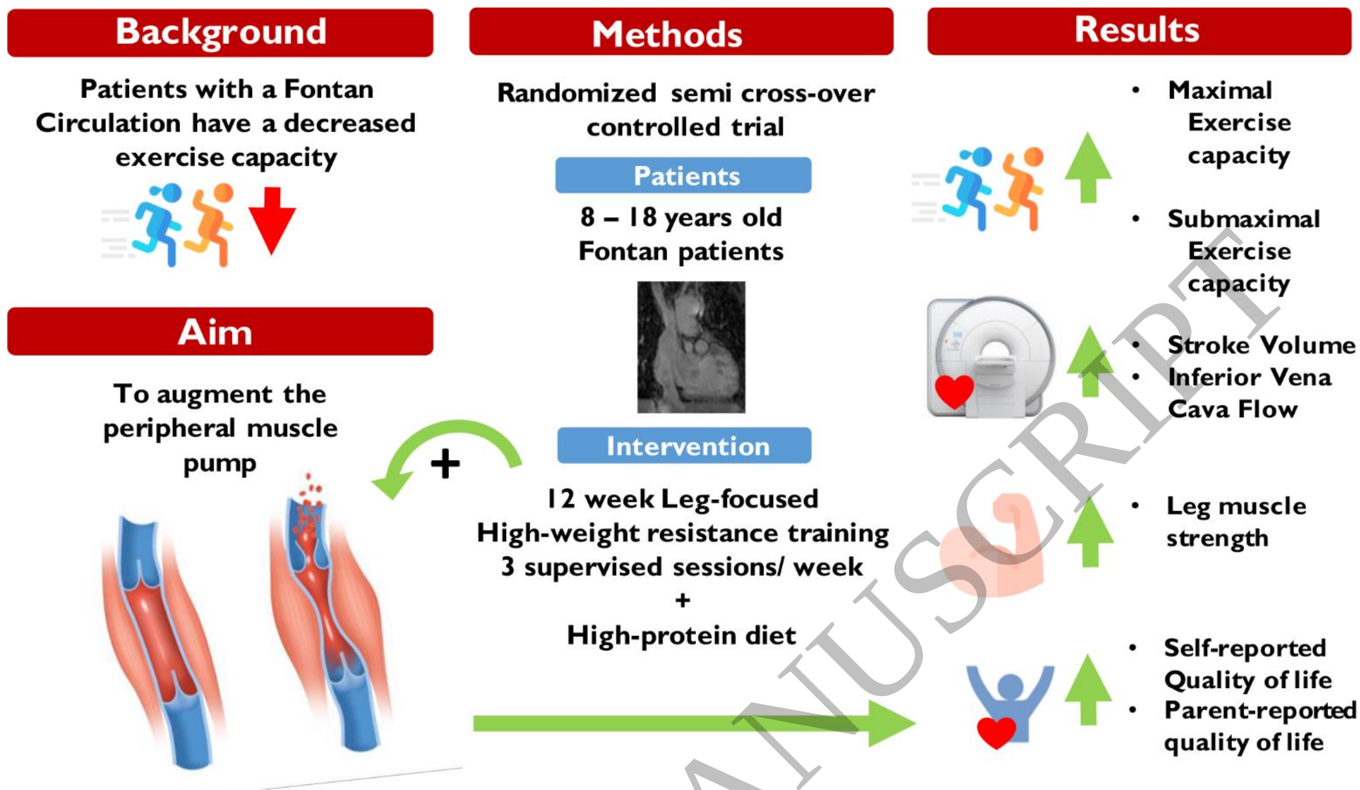
Data is presented as median [IQR] or number (n)/ percentage %. Differences over the exercise period were analyzed using the Wilcoxon signed ranks test or McNemar-bowker test for proportions.

[1]: in one patient aortic insufficiency could not be assessed. This patient was excluded from analysis of flow measurements. Abbreviations: m (meters), ml (milliliters) SVi (indexed stroke volume), EF (Ejection fraction), EDVi (indexed end diastolic volume), ESVi (indexed end systolic volume), SCV (superior caval vein), ICV (inferior caval vein), cm (centimetres), AV (atrioventricular), s (seconds).

Table 4: Core stability and Muscle strength

	Exercise Period (n=28)			Control Period (n=14)				
	Before	After	P-values	Before	After	P-values	Effects size vs control period [95% CI]	P-value difference exercise vs control period
Muscle Strength								
Shoulder abduction (N)	120 [91 – 153]	132 [107 – 198]	**<0.001***	112 [95 – 151]	119 [90 – 151]	0.363	38 [14 – 61]	**0.002***
Elbow flexion (N)	165 [115 – 195]	177 [149 – 230]	**0.002***	139 [119 – 211]	157 [107 – 186]	0.397	26 [9 – 43]	**0.003***
Elbow extension (N)	97 [75 – 139]	103 [80 – 155]	**0.007***	84 [76 – 121]	93 [73 – 113]	0.551	14 [0 – 29]	0.053
Squeezing strength (N)[1]	62 [44 – 99]	67 [46 – 105]	0.143	60 [43 – 98]	62 [43 – 103]	0.600	8 [-6 – 23]	0.248
Hip flexion (N)	221 [175 – 280]	300 [225 – 336]	**<0.001***	208 [187 – 282]	214 [170 – 260]	0.925	72 [42 – 101]	**<0.001***
Hip abduction (N)[2]	137 [104 – 186]	202 [134 – 184]	**0.001***	162 [114 – 183]	137 [106 - 173]	0.331	59 [24 – 93]	**<0.001***
Hip adduction (N)[2]	127 [87 – 149]	165 [134 – 184]	**<0.001***	122 [96 – 164]	128 [84 – 145]	0.258	47 [24 – 70]	**<0.001***
Knee flexion (N)[3]	141 [116 - 174]	157 [121 – 198]	**<0.001***	125 [103 – 148]	131 [111 – 168]	0.861	17 [3 – 31]	**<0.001***
Knee extension (N)	144 [121 - 176]	195 [156 – 242]	**0.006***	135 [111 – 175]	134 [119 – 171]	0.695	50 [24 – 75]	**0.017***
Core stability tests[4]								
Plank (s)	30 [17 – 41]	70 [55 – 84]	**<0.001***	30 [17 – 41]	40 [19 – 64]	0.700	43 [5 – 81]	**0.028***
Side plank left side (s)	12 [6 – 40]	15 [10 – 29]	0.055	15 [9 – 35]	12 [6 – 40]	0.156	8 [-1 – 16]	0.097
Side plank right side (s)	12 [6 – 32]	17 [10 – 28]	0.061	10 [5 – 25]	12 [6 – 32]	0.385	7 [-1 – 14]	0.080
Back bridge (s)	87 [44 – 164]	180 [135 – 300]	**0.001***	84 [38 – 120]	87 [44 – 164]	0.451	108 [12 – 203]	**0.027***

Data is presented as median [IQR]. Differences over the exercise period and control period were analyzed using the Wilcoxon signed ranks test. A generalized equations approach model was used to compare change over the control to the exercise period (described as the effect size including 95% confidence interval (CI) and matching p-value). *= P<0.05. Abbreviations: s (seconds), N (newton). 1: squeezing strength missing in 2 patients n=26, 2: hip adduction/abduction missing in 1 patient n=27. 3: Knee flexion missing in 2 patients in control period, n=12. 4: core stability tests in 2 children are missing, n=26.



Graphical Abstract
178x103 mm (x DPI)