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ORIGINAL ARTICLE

Peak Work Rate Increases With Lower Extremity-Focused Exercise Training in Adolescents With Fontan Circulation

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BACKGROUND: Skeletal muscle deficits are associated with worse exercise performance in the Fontan circulation and may be improved by exercise training. We aimed to assess the change in leg lean mass (a marker of skeletal muscle), exercise performance, and functional health status after a lower extremity-focused exercise intervention in adolescents with Fontan circulation.

METHODS AND RESULTS: Densitometry for measurement of leg lean mass, cardiopulmonary exercise test, exercise cardiac magnetic resonance, peripheral vascular testing, physical activity questionnaire, and quality of life assessment were performed at baseline and after a 24-week, hybrid center- and home-based training program. Leg lean mass Z-scores were generated, and exercise parameters were expressed as percentage expected based on reference data. The effect of training was assessed by paired t-tests and simple linear regression. Twenty participants (15.6±1.7 years, 50% male) demonstrated low baseline leg lean mass Z-scores with no significant improvement with training (–1.38±1.02 pre versus –1.31±1.06 post, P=0.33). Maximum and percent predicted work increased from 121.9±29.8 (0.66±0.12) to 131.3±35.1 (0.70±0.15) watts (P=0.02). Peak respiratory exchange ratio increased (1.19±0.02 versus 1.25±0.01, P=0.02) but percent predicted oxygen consumption was unchanged, suggesting higher anaerobic activity after training. Physical activity questionnaire score positively associated with peak work at baseline (ß=18.13 [95% CI, 0.83–35.44], R^2=0.21; P=0.04) but physical activity questionnaire, quality of life scores, exercise cardiac magnetic resonance performance, and peripheral vascular function were unchanged with training.

CONCLUSIONS: Peak work rate and anaerobic activity increased with lower extremity-focused training in adolescents with Fontan circulation. Larger studies should test the impact of these changes on functional status and quality of life.

Key Words: densitometry ■ exercise ■ Fontan ■ skeletal muscle

Over the past 5 decades, life expectancy has improved for patients with single-ventricle heart disease and Fontan circulation (FC); however, patients face lifelong challenges. Exercise performance may be limited and progressively declines with time,[1,2] contributing to morbidity and poor quality of life. In children with FC, peak oxygen consumption (VO_2) is about 65% predicted for age and sex and begins to worsen in adolescence.[1,2] However, there is marked variability in performance with peak VO_2 ranging from 19% to 112% predicted in cross-sectional analysis.[1] Impaired stroke volume is the primary cardiac determinant of exercise intolerance in the FC, accounting for 73% of predicted peak VO_2,[1] but patients are likely limited by noncardiac factors as well. Without a subpulmonary "pump," pulmonary blood flow and ventricular preload are limited by the inability to raise central venous pressure above a threshold value during exercise. Because of this dependence

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For Sources of Funding and Disclosures, see page 12.

CLINICAL PERSPECTIVE

What is New?

- In a pilot exercise intervention, peak work rate increased with lower extremity-focused training in adolescents with Fontan circulation.
- Peak respiratory exchange ratio increased, but percent predicted oxygen consumption was unchanged, suggesting higher anaerobic activity after this type of focused exercise training.

What Are the Clinical Implications?

- Higher anaerobic activity may confer benefits for accomplishing activities of daily living that are usually performed with short bursts of exertion.
- Our results suggest that exercise training programs for youth with Fontan circulation should incorporate lower extremity-focused light resistance training.

NONSTANDARD ABBREVIATIONS AND ACRONYMS

eCMR	exercise cardiac magnetic resonance
FC	Fontan circulation
LLMZ	Leg lean mass Z-score
PAQ	physical activity questionnaire
Qs	systemic blood flow
VAT	ventilatory anaerobic threshold
VCO_2	carbon dioxide production
VE/VCO_2	ventilatory equivalents of carbon dioxide
VE/VO_2	ventilatory equivalents of oxygen
VO_2	oxygen consumption

on passive filling, we hypothesized that lower extremity skeletal muscle mass is fundamentally important to the FC as its contraction augments systemic venous return and ventricular filling. We previously described marked deficits in densitometry-derived leg lean mass Z-score (LLMZ, a marker of skeletal muscle) in youth with FC in association with worse performance on cardiopulmonary exercise test and exercise cardiac magnetic resonance (eCMR) imaging.[3,4] A small study of adult patients with FC demonstrated improvements in skeletal muscle mass and peak VO_2 with resistance exercise training,[5] suggesting that muscle deficits may be modifiable determinants of exercise performance in the FC. Small pediatric studies have demonstrated some improvements in exercise performance and quality of life with various training regimens,[6–15] but few studies have addressed the physiologic adaptations that result from exercise training in children with FC. To our knowledge, no study has examined the effect of exercise training on lower extremity skeletal muscle mass and other noncardiac factors influencing exercise performance in youth with FC. Therefore, we performed a pilot, dual-center, 24-week lower extremity-focused exercise training intervention in adolescents with FC to assess: (1) the change in LLMZ with the intervention, (2) the change in functional health status as measured by percent-predicted peak VO_2, performance on eCMR, peripheral vascular function, health-related quality of life inventory score, and self-reported physical activity score, and (3) the feasibility of a standardized dual-center training program in youth with FC.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Participants were recruited from the Children's Hospital of Philadelphia (Site 1) and Cincinnati Children's Hospital Medical Center (Site 2). Inclusion criteria were single-ventricle physiology with FC, age 13 to 18 years at the time of study enrollment (to facilitate cooperation with the training program and exercise testing), and height >130 cm (a requirement for cycle ergometry). Exclusion criteria included current pregnancy, metal hardware that interferes with densitometry or eCMR, weight >135 kg (densitometry limit), Fontan baffle obstruction or single-lung physiology, greater than moderate ventricular dysfunction or atrioventricular/semilunar valve stenosis/regurgitation, protein-losing enteropathy, plastic bronchitis, and inability to complete the study procedures attributable to significant developmental delay. Participants with protein-losing enteropathy or plastic bronchitis were excluded as they could deteriorate rapidly over the study period. While geographic proximity to the medical center was not a requirement for study participation, the time and travel commitment were discussed with participants and families before consent. The study was approved by the Institutional Review Boards at both institutions. Fully informed, written consent was obtained from the participant or the parent/legal guardian. In addition, age-appropriate informed assent was obtained from any participant aged <18 years.

Study Procedures

Clinical data including cardiac anatomy, Fontan type, fenestration status, and medications were recorded. There were 2 study visits: at baseline and within 2 weeks of completion of the training program. Study procedures included anthropometry and Tanner stage self-assessment, health-related quality of life and physical activity questionnaires, measurement of vascular function by pulse-wave velocity, whole-body densitometry, cardiopulmonary exercise test, and eCMR. Participants were enrolled between January 2019 and November 2021.

Anthropometry and Tanner Staging

Weight was measured to the nearest 0.1 kg with a digital electronic stand-on scale. Height and sitting height were measured to the nearest 0.1 cm with a wall-mounted stadiometer to calculate leg length (leg length=height – sitting height). Tanner stage was determined via a validated self-assessment tool.[16]

Heath-Related Quality of Life

Participants completed the Pediatric Cardiac Quality of Life Inventory-Adolescent, a reliable and validated instrument of disease-specific quality of life in adolescent heart disease.[17] A total score was generated from the sum of disease impact and psychosocial impact subscores, with higher scores representing better health-related quality of life.

Physical Activity Questionnaire

Participants completed the Physical Activity Questionnaire (PAQ) for Adolescents, a self-administered, 7-day recall instrument that is a valid and feasible measure of assessing moderate to vigorous physical activity in adolescents.[18–20] A series of questions query structured and leisurely physical activity. A 5-point scoring scale is used to generate a final summary score from the means of the activity scores.

Peripheral Vascular Function

Pulse wave velocity was measured using the SphygmoCor CPV System.[21] The average of 3 measures of sternal notch to femoral artery distance was entered into the software. Arterial waveforms gated to the R-wave on the ECG tracing were recorded from the carotid and femoral artery. Pulse wave velocity is the difference in the carotid-to-femoral artery path length divided by the difference in R-wave-to-waveform foot times. Data from the laboratory at Site 2 have shown excellent reproducibility with coefficients of variability <7%, even in obese adolescents.[22]

Densitometry

Whole body and leg lean mass were measured with Hologic Horizon densitometers (Bedford, MA) with a fan beam in the array mode (software version 12.4), excluding the head as we have previously described.[3,4] Measurements were performed with standard supine positioning techniques on participants wearing scrubs as uniform fabric minimizes scan variability. Whole-body lean mass was calculated as fat-free mass minus bone mineral content; leg lean mass was calculated from the right and left leg subregions of the whole-body scan, excluding bone mineral content. Calibration was performed daily with a hydroxyapatite spine phantom and weekly with a whole-body phantom. Data from the laboratory at Site 1 demonstrate coefficients of variation from 1% to 4%.[23]

Cardiopulmonary Exercise Test

Participants were exercised to their maximum ability on an electronically braked cycle ergometer (Site 1: Ergometrics 800, Sensor-Medics, Yorba Linda, CA; Site 2: Corival 400, Lode B.V., Groningen, The Netherlands). Three minutes of pedaling in an unloaded state was followed by a ramp increase in work rate to achieve predicted peak work rate in 10 to 12 minutes of cycling time.[24] A 12-lead ECG was obtained at rest in supine, sitting, and standing positions. Cardiac rhythm and pulse oximetry were monitored throughout the study. Blood pressure was measured at rest and every 3 minutes during exercise and recovery by auscultation. Metabolic data including VO_2, carbon dioxide production (VCO_2), maximum work rate, oxygen pulse, respiratory exchange ratio, and the ventilatory equivalents (VE) of carbon dioxide (VE/VCO_2) and oxygen (VE/VO_2) were obtained throughout the study and for the first 2 minutes of recovery on a breath-by-breath basis using a metabolic cart (Site 1: SensorMedics V29, Yorba Linda, CA; Site 2: Medgraphics, MGC Diagnostics, St Paul, MN). Ventilatory anaerobic threshold (VAT) was measured by the V-slope and dual criteria methods.[25] Peak VO_2 and VO_2 at VAT were normalized to the percentage expected for age, sex, race, and body size.[26] A maximal exercise test was defined as a respiratory exchange ratio ≥1.1.[27]

Exercise Cardiac Magentic Resonance Imaging Analysis

Participants completed a nonsedated resting and eCMR imaging protocol developed by the Site 1 team for use on a supine ergometer.[28] The resting protocol consisted of a contiguous axial stack of static steady-state free precession images used for multiplanar anatomic reconstruction, both segmented and free-breathing real-time cine short-axis stacks, and through-plane retrospectively gated, respiratory-averaged phase-contrast magnetic resonance imaging (MRI) across the superior and inferior vena cavae, descending aorta at the level of the diaphragm, aortic/neo-aortic valve, and branch pulmonary arteries. After resting acquisition, the participant was slid partially out from the MRI bore to perform lower limb exercise using an MRI-compatible supine bicycle ergometer (Lode BV, Groningen, the Netherlands). Heart rate was monitored continuously. The initial workload of 20 watts was increased 20 watts/minute to achieve the heart rate associated with VAT on prior cardiopulmonary exercise test. Exercise was suspended, the participant's feet were removed from the ergometer pedals, and the participant was returned to isocenter for imaging (generally within 5–10 seconds). A free-breathing real-time cine short-axis stack was performed; this method has been previously validated against breath-held segmented short axis imaging.[29,30] As breath holding is not uniform after exercise, respiratory-averaged segmented phase-contrast MRI measurements of the aorta, superior vena cava, and descending aorta were performed. Descending aorta flow is substituted for inferior vena cava flow because of difficulty in maintaining inferior vena cava position at exercise.[31] Flows and volumes were segmented using cvi42 software 5.13.7 (Circle Cardiovascular Imaging Inc.). All eCMR analyses were performed by K.W., masked to participant clinical characteristics and intervention status. Cardiac index was calculated as the product of stroke volume and heart rate, indexed to body surface area. Indexed systemic blood flow (Qs) was calculated as the sum of superior vena cava and descending aorta flow, indexed to body surface area.

Exercise Program

The exercise program was designed by M.M., Supervisor of the Cardiac Rehabilitation Program at Site 1, with extensive experience in exercise training in multiple pediatric heart disease populations.[32–34] The 24-week program consisted of in-person sessions with a trained exercise physiologist and at-home exercises. During the first 4 weeks of the program, participants completed twice-weekly, in-person, 1-hour exercise training sessions (8 sessions total) in the centers' exercise laboratories. Thereafter, participants returned for monthly, in-person, 1-hour exercise training sessions during weeks 8, 12, 16, 20, and 24 (5 additional sessions). The in-person sessions began with stretching and brief aerobic warm-up exercises. Participants completed circuits of resistance exercises with at least 75% concentrated on the lower limbs and the remaining exercises concentrated on the upper limbs and torso to maintain body habitus. Resistance training intensity (weight) was maintained at 60% of pretraining maximal voluntary contraction for each muscle group. Constant weight was maintained throughout the program to control for the wide heterogeneity of participants with FC and to alleviate the need for participants to purchase additional weights and equipment, especially as the COVID-19 pandemic ensued. The participants completed 1 repetition every 3 seconds (15 repetitions/minute) and were instructed in the correct lifting and breathing technique to avoid the Valsalva maneuver. Participants graded each exercise as "easy," "medium," or "hard" as they proceeded through the circuit. As the participants progressed through the program, we personalized an increase in repetitions if they reported that the exercise regimen became too easy. Cool-down exercises concluded the sessions. Vital signs were monitored intermittently.

Participants were taught home exercises similar to those performed in the in-person sessions; these did not require the purchase of any weights or equipment. Paper handouts describing the exercises were provided. Participants received a weekly "schedule" with 9 to 12 exercises and were encouraged to perform the exercises 3 times per week at home. They received diaries in which to record their home exercise as well as any additional physical activity; ideally a participant should have reported 72 home exercise sessions if they engaged in the program for 24 weeks. At monthly in-person sessions, the exercise physiologist asked the participant to demonstrate the home routine to judge whether they were exercising at home. A study team member contacted participants weekly to encourage adherence, assess for adverse events, and answer any study-related questions.

The COVID-19 pandemic began approximately halfway through this study. Research activities were halted and then severely restricted at both institutions between March 2020 and August 2020 and again from November 2020 to December 2020 in Philadelphia, PA. Participants who were in the midst of the training program (Site 1 only) were unable to attend monthly in-person sessions at the hospital, so participants and trainers engaged via the BlueJeans remote meeting platform to complete monthly supervised sessions. Participants continued home exercise during this time. Participants who were due to complete the second study visit during the shut-down were instructed to continue home exercise and meet with the trainers monthly until their second visit could be scheduled.

Statistical Analysis

Growth and body composition variables were converted to Z-scores (SD scores). The 2000 Centers for Disease Control and Prevention growth charts were used to calculate sex-specific Z-scores for height, weight, and body mass index relative to age.[35] Data from >2000 healthy, typically developing children from multiple ethnic groups, ages 5 to 19 years, enrolled in the Bone Mineral Density in Childhood Study,[36,37] a multicenter longitudinal densitometry study, were used to compare participants' growth Z-scores to a contemporary cohort. These reference data were also used to calculate sex- and race-specific LLMZs relative to age using the Lambda-Mu-Sigma method. Body composition measures are highly correlated with height, and the FC is associated with impaired linear growth. Therefore, LLMZ was further adjusted for leg length Z-score.[38]

Standard descriptive statistics were used to summarize baseline characteristics, LLMZ, PAQ and quality of scores, vascular function, and exercise parameters. Paired t-tests were conducted to assess changes following the exercise program. To preliminarily explore whether changes in exercise performance over the 2 time points reflected changes in LLMZ or physical activity, separate simple linear regression models were developed to examine the effect of LLMZ or PAQ score changes on changes in measures of exercise performance.

Based on funding considerations, this pilot study was expected to enroll 20 participants. Assuming a pre-intervention mean LLMZ of −0.89 and an SD of 0.91 based on our preliminary data,[3] a sample size of 20 could detect a difference in mean LLMZ of 0.64 after intervention with 85% power using a paired *t*-test at 0.05 level of significance. Assuming an SD of 6.9 mL/kg/min for VO_2 at peak exercise,[1] a sample size of 20 could detect a VO_2 change of 4.9 mL/kg/min. In the original study design, only participants at Site 1 were to perform eCMRs. Therefore, given an SD of 1.3 L/min/m^2 for exercise cardiac index and 0.9 L/min/m^2 for exercise Qs,[4] a sample size of 10 could detect changes of 1.4 L/min/m^2 and 1 L/min/m^2, respectively. Funding and other considerations later enabled performance of eCMRs at both sites.

RESULTS

Recruitment materials were sent to a total of 103 potential participants at the 2 sites. Four potential participants were deemed ineligible based on inclusion/exclusion criteria. Nine potential participants declined to consent because of concerns over study procedures, distance traveled for in-person exercise sessions, or time commitment. Seventy potential participants never responded or did not follow-up on initial interest. We enrolled 20 participants with a consent rate of 19%.

Demographic and clinical characteristics of the 20 participants are detailed in Table 1. Seventy-five percent of the cohort was recruited from Site 1. The cohort was evenly split between males and females and majority non-Hispanic White. Participants were relatively well with a low medication requirement, and most had preserved ventricular function and no more than mild atrioventricular or semilunar valve regurgitation on most recent echocardiogram. There were

Table 1. Summary of Study Participants Demographic and Clinical Characteristics Data (N=20)

Variable	n (%) or mean±SD
Age at beginning of study, y	15.6±1.7
Site	
Site 1	15 (75%)
Site 2	5 (25%)
Sex	
Female	10 (50%)
Male	10 (50%)
Race and ethnicity	
Non-Hispanic White	15 (75%)
Non-Hispanic Black	4 (20%)
Asian	1 (5%)
Anatomy	
Hypoplastic left heart syndrome	7 (35%)
Tricuspid atresia	4 (20%)
Double outlet right ventricle	4 (20%)
Unbalanced atrioventricular canal	1 (5%)
Pulmonary atresia	1 (5%)
Other	3 (15%)
Systemic ventricle	
Right	11 (55%)
Left	9 (45%)
Heterotaxy syndrome	1 (5%)
Time from Fontan, y	11.7±3.4
Type of Fontan	
Extra-cardiac conduit	14 (70%)
Lateral tunnel	6 (30%)
Fenestration present at the time of initial operation	19 (95%)
Medications	
Udenafil	5 (25%)
Sildenafil	2 (10%)
Enalapril	8 (40%)
Aspirin	20 (100%)
Vitamin D supplementation	1 (5%)
Ventricular function by most recent echocardiogram	
Normal to mildly diminished	10 (95%)
Moderately diminished	1 (5%)
Atrioventricular valve regurgitation by most recent echocardiogram	
None to mild	15 (75)
Moderate	5 (25%)
Aortic or neo-aortic regurgitation by most recent echocardiogram	
None to mild	20 (100%)
Number of at-home exercise sessions reported*	69 (range 25–105)
Weeks between pre- and post-intervention testing	32.1±7.7

*Only 14 participants completed the home exercise diaries.

5 participants on udenafil as they were enrolled in the open-label extension phase of the FUEL (Fontan Udenafil Exercise Longitudinal) trial[39,40] during this pilot exercise intervention.

All participants attended the 13 planned "in-person" sessions with the trainers either at the center or via BlueJeans, as above. Fourteen participants (70%) completed home exercise diaries. The average number of home sessions reported was 69, but this ranged from 25 to 105 as some participants were engaged in the program for more than 24 weeks given the COVID-19 pandemic (average number of weeks 32.1±7.7). There were no adverse events reported.

Height, weight, and body mass index Z-scores were relatively normal in this cohort of participants with FC. Pre- and post-intervention LLMZ were measured in 19 participants. Unfortunately, sitting height was not measured in one participant so baseline leg length and LLMZ could not be measured. A technical challenge with the SphygmoCor system prevented baseline measurement of pulse wave velocity in one participant. A mass flow sensor malfunction prevented measurement of post-intervention maximal aerobic capacity in 1 participant. Claustrophobia prevented 1 participant from performing baseline eCMR but the participant completed the post-intervention eCMR with further education about the CMR process. Coil artifact prevented calculation of caval flow in 2 participants. The exercise, real-time ventricular volumes could not be analyzed in 5 participants because of excessive artifact.

Pre- and post-intervention data are displayed in Table 2. Percent predicted peak VO_2 and VO_2 at VAT were about 0.72 and 0.78, respectively, and did not change with the intervention. With exercise training, maximum work rate increased from 121.90±29.82 watts to 131.25±35.12 watts (P=0.02) and percent predicted work rate increased from 0.66±0.12 to 0.70±0.15 (P=0.02) (Figure). The respiratory exchange ratio at peak exercise increased from 1.19±0.02 to 1.25±0.01 (P=0.02). There was no change in LLMZ, PAQ, or quality of life scores, pulse wave velocity, or eCMR performance with exercise training. There were no differences in pre- and post-intervention LLMZ, percent predicted VO_2, percent predicted work rate, or eCMR performance by sex, completion of home exercise diaries, number of home exercise sessions reported, or completion of training relative to the start of the COVID-19 pandemic. Baseline associations between LLMZ, physical activity, and exercise performance are shown in Table 3. At baseline, there was a positive association between LLMZ and percent predicted peak VO_2 (ß 0.11 [95% CI, 0.06–0.17], R^2=0.52; P<0.001), peak work rate (ß 18.06 [95% CI, 6.04–30.07], R^2=0.37; P=0.006), and resting, exertional, and change in Qs (resting Qs: ß 0.65 [95% CI, 0.30–1.00], R^2=0.51; P=0.001), (exercise Qs: ß 1.53 [95% CI, 0.80–2.26], R^2=0.59; P<0.001), (change in Qs from rest to exercise: ß 0.82 [95% CI, 0.17–1.47], R^2=0.34; P=0.02). There was a trend toward association between LLMZ and exercise cardiac index, but this did not reach statistical significance.

At baseline, there was a positive association between PAQ score and peak work rate (ß 18.13 [95% CI, 0.83–35.44], R^2=0.21; P=0.04) and change in cardiac index from rest to exertion (ß 0.77 [95% CI, 0.16–1.38], R^2=0.39; P=0.02). There was a negative association between PAQ score and ventilatory efficiency for carbon dioxide (VE/VCO_2) at VAT (ß −2.74 [95% CI, −4.66 to −0.81], R^2=0.33; P=0.008). There were trends toward association between PAQ score and percent predicted peak VO_2 and percent predicted work rate, but these did not reach statistical significance. There was no association between PAQ score and LLMZ.

Training-related associations are shown in Table 4. The observed change in LLMZ with training was associated with a positive change in resting stroke volume (ß 13.90 [95% CI, 0.01–27.79], R^2=0.22; P=0.05) and resting cardiac index (ß 1.24 [95% CI, 0.10–2.37], R^2=0.27; P=0.03). There were trends in association between observed change in LLMZ and change in percent predicted peak VO_2 and change in Qs, but these did not reach statistical significance. The larger changes in LLMZ with training were associated with reduced changes in both cardiac index (ß −2.34 [95% CI, −4.02 to −0.67], R^2=0.44; P=0.01) and ejection fraction (ß −15.58 [95% CI, −30.95 to −0.20], R^2=0.29; P=0.05), which were directionally inconsistent.

There were trends in association between change in PAQ score and change in percent predicted VO_2 at VAT, change in work rate at VAT, and change in exercise cardiac index, but these did not reach statistical significance. There was no association between change in PAQ score and change in LLMZ.

DISCUSSION

In this pilot study, participants with FC engaged in a lower extremity-focused exercise training program achieved a higher work rate, indexed for age, sex, race, and body size. Percent predicted peak VO_2 and percent predicted peak VO_2 at VAT were maintained across the duration of the intervention but respiratory exchange ratio at peak exercise increased, suggesting increased aerobic metabolism. At baseline, higher LLMZ was associated with better exercise performance, consistent with our previous findings in this population. There was no significant increase in LLMZ with training; however, the observed change in LLMZ was associated with an increase in percent predicted peak VO_2 of borderline statistical significance. Despite the COVID-19 pandemic, we implemented a successful

Table 2. Comparison of Study Outcomes Pre- and Post-Intervention

Variable	n	Pre-intervention (mean±SD)	Post-intervention (mean±SD)	Change score (mean±SD)	*P* value*
Height Z-score	20	−0.04±0.84	−0.05±0.86	−0.01±0.19	0.76
Weight Z-score	20	−0.01±0.93	−0.01±0.95	0.00 ±0.21	0.94
Body mass index Z-score	20	−0.08±1.01	−0.12±1.14	−0.03 ±0.27	0.58
LLMZ	19	−1.38±1.02	−1.31±1.06	0.07±0.30	0.33
PAQ score	20	2.30±0.76	2.09±0.92	−0.21±0.97	0.33
Child quality of life score	20	65.73±20.73	65.45±16.84	−0.28±14.95	0.93
Parent quality of life score	20	64.43±19.71	67.66±19.97	3.23±10.67	0.19
Pulse wave velocity (m/s)	19	4.22±0.91	4.23±0.91	0.01±0.93	0.98
Cardiopulmonary exercise testing					
Rest					
Heart rate (bpm)	20	88.00±15.77	83.85±15.83	−4.15±13.76	0.19
Systolic blood pressure (mm Hg)	20	110.50±11.69	112.70±8.99	2.20±11.89	0.42
Diastolic blood pressure (mm Hg)	20	63.80±7.80	69.25±8.62	5.45±7.63	0.005
Oxygen saturation (%)	20	92.50±3.35	93.00±3.32	0.50±2.16	0.31
Peak exercise performance					
Heart rate (bpm)	20	174.65±10.33	176.80±9.25	2.15±5.28	0.08
Systolic blood pressure (mm Hg)	20	147.65±11.85	152.30±18.70	4.65±11.49	0.09
Diastolic blood pressure (mm Hg)	19	61.58±7.13	63.68±10.82	2.11±9.79	0.36
Oxygen saturation (%)	20	89.30±4.91	90.00±4.52	0.70±3.18	0.34
VO_2 (mL/kg/min)	19	28.43±5.55	28.93±5.58	0.50±4.10	0.60
Percent predicted VO_2	19	0.72±0.16	0.71±0.14	−0.02±0.15	0.65
VCO_2 (mL/kg/min)	19	34.96±7.20	35.77±7.36	0.81±5.72	0.54
Work (watts)	20	121.90±29.82	131.25±35.12	9.35±16.40	0.02
Percent predicted work	20	0.66±0.12	0.70±0.15	0.04±0.07	0.02
Ventilatory measures at peak exercise					
Maximum minute ventilation (L/min)	19	79.31±27.85	83.69±30.45	4.38±15.35	0.23
Tidal volume (L)	19	1.44±0.51	1.52±0.52	0.08±0.20	0.09
Maximum respiratory rate (breaths/min)	18	56.17±15.22	55.06±10.89	−1.11±9.90	0.64
Breathing reserve (%)	14	28.86±22.42	27.21±22.69	−1.64±15.36	0.70
Respiratory exchange ratio	19	1.19±0.02	1.25±0.01	0.06±0.03	0.02
Performance at VAT					
Heart rate (bpm)	20	136.25±21.01	136.50±17.59	0.25±14.61	0.94
VO_2 (mL/kg/m^2)	20	18.39±2.67	18.20±3.12	−0.18±2.78	0.77
Percent predicted VO_2	20	0.78±0.17	0.79±0.16	0.01±0.14	0.82
VCO_2 (mL/kg/m^2)	20	18.16±2.71	18.61±3.17	0.45±2.72	0.47
Work (watts)	20	62.85±19.35	64.50±21.41	1.65±18.44	0.69
Ventilatory measures at VAT					
Maximum minute ventilation (L/min)	20	35.30±7.26	37.33±8.11	2.03±7.56	0.25
Tidal volume (L)	20	1.16±0.46	1.14±0.38	−0.02±0.20	0.69
Respiratory rate (breaths/min)	20	33.40±12.95	35.55±11.74	2.15±7.73	0.23
VE/VO_2	20	34.20±3.81	35.25±6.09	1.05±7.25	0.52

(Continued)

Table 2. Continued

Variable	n	Pre-intervention (mean±SD)	Post-intervention (mean±SD)	Change score (mean±SD)	*P* value*
VE/VCO_2	20	34.70±3.60	34.60±4.89	−0.10±5.57	0.94
Respiratory exchange ratio	20	0.99±0.04	1.02±0.07	0.04±0.10	0.11
CMR data					
Rest					
Caval flow, Qs ($L/min/m^2$)	18	4.79±0.88	4.94±1.33	0.15±0.76	0.42
Stroke volume (cc/m^2)	19	50.92±10.63	52.43±11.77	1.51±8.99	0.47
Cardiac index ($L/min/m^2$)	18	3.71±0.70	3.83±0.66	0.12±0.70	0.47
Ejection fraction (%)	19	60.35±9.03	59.21±8.71	−1.14±7.54	0.52
Exercise					
Caval flow, Qs ($L/min/m^2$)	17	7.95±1.99	7.72±2.02	−0.22±1.12	0.42
Stroke volume (cc/m^2)	14	54.23±8.20	56.45±8.59	2.22±9.94	0.42
Cardiac index ($L/min/m^2$)	14	5.48±0.91	5.38±0.82	−0.10±0.94	0.69
Ejection fraction (%)	14	65.24±8.17	63.24±6.97	−2.01±6.77	0.29
Change from rest to exercise					
Caval flow, Qs ($L/min/m^2$)	17	3.16±1.43	2.84±1.62	−0.32±1.37	0.35
Stroke volume (cc/m^2)	14	15.39±15.81	15.56±10.81	0.16±14.72	0.97
Cardiac index ($L/min/m^2$)	14	1.71±0.96	1.69±1.24	−0.02±1.22	0.95
Ejection fraction (%)	14	8.17±7.12	5.76±7.88	−2.41±9.94	0.38

CMR indicates cardiac magnetic resonance; LLMZ, leg lean mass Z-score; PAQ, physical activity questionnaire; Qs, systemic flow; VAT, ventilatory anaerobic threshold; VCO_2, carbon dioxide production; VE/VCO_2, minute ventilation/minute carbon dioxide production; VE/VO_2, minute ventilation/minute oxygen consumption; and VO_2, oxygen consumption.

**P* values were not adjusted for multiple comparison correction as this was a pilot study.

hybrid hospital-home program supplemented by a virtual meeting platform.

Exercise training has emerged as a promising intervention to improve performance in youth with FC. Multiple studies have demonstrated the safety and feasibility of hospital-based programs as well as the incorporation of home training.[6–15] Previous investigators have achieved various improvements in peak VO_2, cardiorespiratory function, physical activity levels, and quality of life. However, programs have varied by exercise type (aerobic, resistance, and inspiratory muscle training), duration, setting, parental involvement, age and Tanner stage at training, and targeted mechanism; therefore, the optimal training regimen remains unknown. We previously

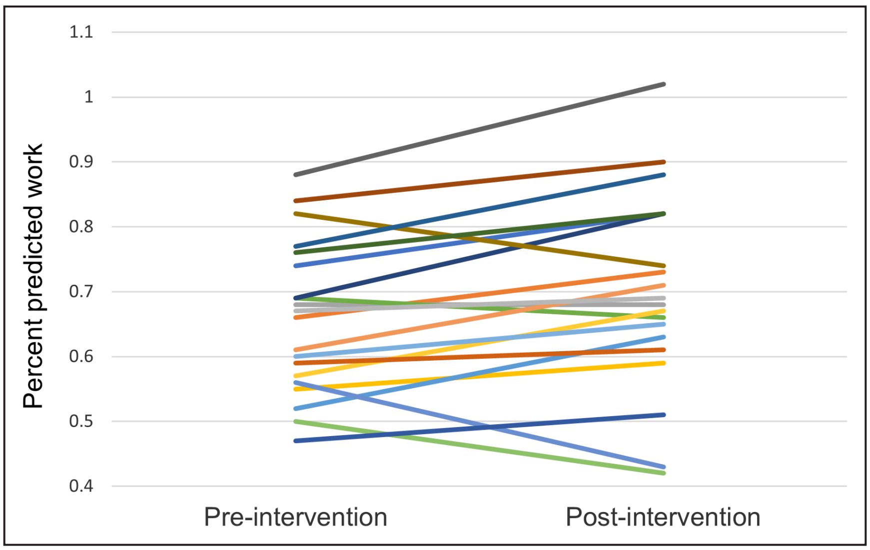

Figure. Change in percent predicted work with lower extremity-focused exercise intervention.

Table 3. Baseline Unadjusted Associations Between LLMZ, PAQ, and Exercise Performance

	Coeff (95% CI)	R^2	*P* value*
LLMZ and:†			
Percent predicted VO_2	0.11 (0.06 to 0.17)	0.52	<0.001
Percent predicted VO_2 at VAT	0.02 (−0.07 to 0.11)	0.01	0.66
Peak work	18.06 (6.04 to 30.07)	0.37	0.006
Percent predicted work	0.04 (−0.02 to 0.10)	0.12	0.14
Work at VAT	4.67 (−4.91 to 14.24)	0.06	0.32
VE/VO_2 at VAT	0.75 (−1.16 to 2.65)	0.04	0.42
VE/VCO_2 at VAT	0.15 (−1.70 to 1.99)	<0.01	0.87
Resting Qs	0.65 (0.30 to 1.00)	0.51	0.001
Resting stroke volume	2.14 (−3.34 to 7.62)	0.04	0.42
Resting cardiac index	0.00 (−0.36 to 0.37)	<0.01	0.98
Resting ejection fraction	−1.59 (−6.36 to 3.19)	0.03	0.49
Exercise Qs	1.53 (0.80 to 2.26)	0.59	<0.001
Exercise stroke volume	−2.85 (−9.07 to 3.38)	0.08	0.34
Exercise cardiac index	0.55 (−0.08 to 1.18)	0.23	0.08
Exercise ejection fraction	2.48 (−3.78 to 8.74)	0.06	0.4
Change in Qs	0.82 (0.17 to 1.47)	0.34	0.02
Change in stroke volume	−0.81 (−13.28 to 11.66)	<0.01	0.89
Change in cardiac index	0.44 (−0.26 to 1.15)	0.14	0.19
Change in ejection fraction	1.73 (−3.78 to 7.25)	0.04	0.51
Pulse wave velocity	−0.05 (−0.55 to 0.45)	<0.01	0.84
PAQ score and:‡			
Percent predicted VO_2	0.09 (0.00 to 0.19)	0.18	0.06
Percent predicted VO_2 at VAT	0.05 (−0.06 to 0.16)	0.04	0.37
Peak work	18.13 (0.83 to 35.44)	0.21	0.04
Percent predicted peak work	0.07 (0.00 to 0.14)	0.18	0.06
Work at VAT	4.36 (−8.10 to 16.82)	0.03	0.47
VE/VO_2 at VAT	−2.83 (−4.89 to −0.78)	0.32	0.01
VE/VCO_2 at VAT	−2.74 (−4.66 to −0.81)	0.33	0.008
Resting Qs	0.38 (−0.17 to 0.94)	0.12	0.16
Resting stroke volume	5.37 (−1.06 to 11.80)	0.15	0.10
Resting cardiac index	−0.07 (−0.51 to 0.38)	<0.01	0.76
Resting ejection fraction	1.42 (−4.48 to 7.31)	0.01	0.62
Exercise Qs	1.00 (−0.22 to 2.22)	0.17	0.10
Exercise stroke volume	2.95 (−3.46 to 9.37)	0.08	0.34
Exercise cardiac index	0.40 (−0.30 to 1.10)	0.11	0.24
Exercise ejection fraction	−1.81 (−8.36 to 4.74)	0.03	0.56
Change in Qs	0.62 (−0.28 to 1.52)	0.13	0.16
Change in stroke volume	3.51 (−9.16 to 16.18)	0.03	0.56
Change in cardiac index	0.77 (0.16 to 1.38)	0.39	0.02
Change in ejection fraction	−1.68 (−7.38 to 4.02)	0.03	0.53
Pulse wave velocity	−0.28 (−0.87 to 0.30)	0.06	0.32
PAQ score and LLMZ§	0.33 (−0.36 to 1.02)	0.06	0.33

(*Continued*)

Table 3. Continued

LLMZ indicates leg lean mass Z-score; PAQ, physical activity questionnaire; Qs, systemic flow; VAT, ventilatory anaerobic threshold; VE/VCO_2, minute ventilation/minute carbon dioxide production; VE/VO_2, minute ventilation/minute oxygen consumption; and VO_2, oxygen consumption.

**P* values were not adjusted for multiple comparison correction as this was a pilot study.

†Leg lean mass Z-score as predictor.

‡Physical activity questionnaire score as predictor.

§Physical activity questionnaire score as predictor.

described the association between LLMZ and exercise performance in adolescents with FC,[4] which led to the hypothesis that augmentation of the lower extremity muscle pump could improve performance in this group and provided support for this targeted intervention. Other investigators have also studied the importance of the skeletal muscle pump in FC.[13,41] Pyykkonen recently demonstrated baseline associations between peak VO_2 and leg muscle mass assessed by bioimpedance in adolescents with FC.[13] Like our study, neither peak VO_2 nor leg muscle mass increased after a 6-month training program; however, work tolerance increased in both studies. In Pyykkonen's study, the association between peak VO_2 and leg muscle mass was maintained with training. Cordina also described the association between skeletal muscle deficits and worse exercise performance in adult patients with FC and demonstrated increased calf muscle mass and higher peak VO_2 with resistance muscle training in a small number of older patients.[5] Our findings support this prior experience that lower extremity training is an important consideration in FC; larger studies may demonstrate an increase in muscle mass or efficiency with training.

Peak VO_2 is most commonly used to represent functional exercise capacity as a coordination of the circulatory, respiratory, and skeletal muscle systems. However, multiple other measures including maximum work rate correlate with survival in healthy populations as well as those with heart failure in biventricular circulation.[42]

Table 4. Univariate associations between change in PAQ or LLMZ and change in performance

	Coeff (95% CI)	R^2	*P* value*
Change in LLMZ and change in:†			
Percent predicted VO_2	0.23 (−0.01 to 0.48)	0.2	0.06
Percent predicted VO_2 at VAT	−0.02 (−0.26 to 0.21)	<0.01	0.83
Peak work	4.93 (−23.42 to 33.28)	<0.01	0.72
Percent predicted peak work	0.08 (−0.04 to 0.20)	0.11	0.16
Work at VAT	−6.22 (−38.00 to 25.56)	<0.01	0.68
VE/VO_2 at AT	−6.00 (−18.18 to 6.19)	0.06	0.31
VE/VCO_2 at AT	−4.32 (−13.74 to 5.10)	0.05	0.35
Resting Qs	1.04 (−0.19 to 2.28)	0.18	0.09
Resting stroke volume	13.90 (0.01 to 27.79)	0.22	0.05
Resting cardiac index	1.24 (0.10 to 2.37)	0.27	0.03
Resting ejection fraction	8.35 (−4.11 to 20.81)	0.11	0.17
Exercise Qs	1.00 (−0.99 to 2.98)	0.08	0.30
Exercise stroke volume	4.69 (−13.30 to 22.68)	0.03	0.58
Exercise cardiac index	−0.17 (−1.90 to 1.55)	<0.01	0.83
Exercise ejection fraction	2.50 (−9.81 to 14.81)	0.02	0.67
Change in Qs	−0.22 (−2.73 to 2.30)	<0.01	0.86
Change in stroke volume	13.23 (−12.46 to 38.91)	0.09	0.28
Change in cardiac index	−2.34 (−4.02 to −0.67)	0.44	0.01
Change in ejection fraction	−15.58 (−30.95 to −0.20)	0.29	0.05
Pulse wave velocity	−0.30 (−2.00 to 1.39)	<0.01	0.71
Change in PAQ score and change in:‡			
Percent predicted VO_2	0.05(−0.02 to 0.13)	0.12	0.14
Percent predicted VO_2 at VAT	0.06(−0.00 to 0.12)	0.17	0.07
Peak work	4.42(−3.70 to 12.54)	0.07	0.27
Percent predicted peak work	0.03 (−0.01 to 0.06)	0.13	0.13
Work at VAT	7.45(−1.26 to 16.16)	0.15	0.09
VE/VO2 at AT	−1.24(−4.91 to 2.42)	0.03	0.48
VE/VCO2 at AT	−0.55(−3.40 to 2.29)	<0.01	0.69
Resting Qs	−0.13(−0.53 to 0.26)	0.03	0.48
Resting stroke volume	3.25(−1.10 to 7.60)	0.13	0.13
Resting cardiac index	0.08(−0.30 to 0.46)	0.01	0.67
Resting ejection fraction	0.07(−3.84 to 3.98)	<0.01	0.97
Exercise Qs	0.31(−0.26 to 0.88)	0.08	0.26
Exercise stroke volume	1.67(−5.33 to 8.67)	0.02	0.61
Exercise cardiac index	0.56(−0.02 to 1.13)	0.27	0.06
Exercise ejection fraction	−0.99(−5.77 to 3.79)	0.02	0.66
Change in Qs	0.45(−0.24 to 1.13)	0.11	0.19
Change in stroke volume	−3.86(−14.06 to 6.34)	0.05	0.43
Change in cardiac index	0.20(−0.65 to 1.06)	0.02	0.61
Change in ejection fraction	−0.73(−7.80 to 6.34)	<0.01	0.83
Pulse wave velocity	−0.32(−0.77 to 0.14)	0.11	0.16
Change in PAQ score and change in LLMZ§	0.02(−0.13 to 0.18)	<0.01	0.75

LLMZ indicates leg lean mass Z-score; PAQ, physical activity questionnaire; Qs, systemic flow; VAT, ventilatory anaerobic threshold; VE/VCO_2, minute ventilation/minute carbon dioxide production; VE/VO_2, minute ventilation/minute oxygen consumption; and VO_2, oxygen consumption.

**P* values were not adjusted for multiple comparison correction as this was a pilot study.

†Change in leg lean mass Z-score as predictor.

‡Change in physical activity questionnaire score as predictor.

§Change in physical activity questionnaire score as predictor.

Exercise training programs in youth with FC have demonstrated improvements in both maximal and submaximal exercise performance and work rate.[12,43] In our study, the increase in work rate with unchanged peak VO_2 and higher respiratory exchange ratio suggests that lower extremity-focused, light resistance training promotes anaerobic metabolism in patients with FC. This may confer benefits for accomplishing activities of daily living that are usually performed with short bursts of exertion. This could improve quality of life for patients with FC if sustained for longer periods. While we did not demonstrate increased muscle mass with training, higher work rate may reflect increased muscle fitness and strength,[15] as in Pyykkonen's study where exercise training resulted in increased work rate and muscle strength measured by standing long jump and shuttle run test.[13] Future studies should investigate the effect of these improvements in strength on disease progression and symptoms. Additional work is needed to understand whether interventions to augment muscle mass and strength earlier in childhood could improve anaerobic power and overall fitness before many patients with FC decline in adolescence and young adulthood. As we saw variable improvement in work rate in the cohort, future studies should examine the factors associated with positive response to a lower extremity-focused training program.

Our study also adds unique value to existing literature by assessing both leg muscle mass and exercise performance relative to reference data in patients with FC. Most body composition parameters vary by age, sex, race, and body size (height) so it is crucial to generate Z-scores, especially in a population with impaired growth such as those with FC. Interestingly the height Z-score in this sample was nearly 0, reflecting normal average height. This contrasts with our previous work in patients with FC[3,4] and may reflect the tendency of healthier patients with FC to voluntarily engage in exercise training. This is the first Fontan exercise trial to express peak VO_2, VO_2 at VAT, and maximum work rate as percent predicted for age, sex, race, and body size using reference values from more than 1800 healthy US children published by members of our study team.[26] Indexing performance measures (including work rate) to body size is critical, especially during a global pandemic with the potential for weight gain during the intervention period. Our study population was similar to the reference sample, which encompassed a diverse suburban and urban population with 90% White or Black youth. Our approach allows normative values to be more specific for the individual participant's characteristics.

The COVID-19 pandemic began about halfway through this study, substantially affecting the plan for in-person training sessions and increasing the study duration in some participants who were unable to return to the hospital for their post-intervention testing. We pivoted and used a remote meeting platform to maintain engagement with the participants, follow training progress, and observe some exercise sessions. This experience demonstrated the feasibility of virtual platforms to deliver exercise interventions in patients with FC and provides support for future home-based trials. COVID-19 had damaging effects on mental health and physical activity levels in many people, and several studies have demonstrated the effects in healthy children[44] and those with congenital heart disease.[45–47] Neither quality of life nor PAQ scores increased with our intervention. However, like other studies during the pandemic,[48] we cannot separate the potential benefits of exercise from the negative effects of the COVID-19 pandemic. Perhaps participants were able to maintain their quality of life and activity levels during a global pandemic through engagement in an exercise program.

Quantification of physical activity is critical to the development of exercise interventions in the FC. Most studies, including ours, have assessed activity by self-reported questionnaire. Longmuir's study was unique in the use of hip-worn accelerometers to measure physical activity in participants with FC and demonstrated increased physical activity intensity post intervention.[11] In the current study, we demonstrated baseline associations between PAQ score and both peak VO_2 and VE/VCO_2, a marker of ventilatory efficiency. A higher PAQ score was associated with higher peak VO_2, while a lower PAQ score was associated with higher VE/VCO_2 (a poor prognostic sign). Pyykkonen also demonstrated a positive association between physical activity questionnaire score and peak VO_2 at baseline, although neither increased with exercise training.[13] Elevated VE/VCO_2 is associated with worse prognosis in heart failure with preserved ejection fraction as well as pulmonary hypertension with right heart failure.[49] Wittekind demonstrated improvement in VE/CO_2 in participants with FC after a 12-week training program,[8] although they did not measure reported activity levels. Our results also suggest that increased physical activity could contribute to more efficient ventilation and improved exercise capacity in the FC.

Our study has several limitations, some of which have been mentioned above. The lack of a control group prevents understanding whether non-trained patients with FC may have demonstrated a decline in exercise performance in the same period. This type of exercise training may slow the decline in patients without an intervention. There may also be inclusion bias as healthier patients with FC could be more likely to engage in an exercise program. Sicker patients may experience greater benefits from exercise rehabilitation. Additionally, more complete demographic information is necessary to understand whether this cohort is a representative sample of patients with FC or includes patients from more educated, higher income, and more resourced families who are more likely to engage in cardiac rehabilitation programs. One-quarter of the participants were enrolled in a medical intervention to improve exercise performance (FUEL open-label extension), which may have biased results. Physical activity was assessed by self-reported questionnaire. While this is a well-validated measure, future studies will be strengthened by directly measuring activity by wearable accelerometer devices. Additionally, completion of exercise diaries was poor, making it difficult to assess compliance with home training. The lack of association between LLMZ and eCMR measures may have been attributable to the small sample size as some participants' CMR data could not be interpreted because of motion or metal artifact, speaking to the technical challenges of implementing an eCMR protocol across 2 centers. We did not use statistical correction for the multiple comparisons presented in our analyses because this was a pilot study, and the analyses were exploratory. Finally, the COVID-19 pandemic was an unexpected hurdle, but participants did demonstrate some improvements in exercise performance, despite the devastating effects on everyone's lives. The COVID-related interruptions to the program may have prevented improvement in LLMZ and other measures of exercise performance with training. The pandemic decreased the number of in-person sessions we could complete and caused heterogeneity in training time. The pandemic may have also affected patient time and resources, resulting in the wide range of reported home sessions. These factors likely affected the intervention efficacy. A more consistent training period with increased objective assessment may be necessary to augment skeletal muscle mass and exercise performance in patients with FC.

In conclusion, adolescents with FC demonstrated higher peak work rate after a 24-week lower extremity-focused exercise training program. Higher respiratory exchange ratio but unchanged peak VO_2 suggested improved anaerobic metabolism. Small increases in skeletal muscle mass, as measured by densitometry-derived LLMZ, were associated with higher peak VO_2. A hybrid model of hospital and home-based training, enriched by a mobile meeting platform, was feasible and effective despite the global COVID-19 pandemic. Larger studies should test the impact of these improvements on functional status and quality of life in this population.

ARTICLE INFORMATION

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REFERENCES

1. Paridon SM, Mitchell PD, Colan SD, Williams RV, Blaufox A, Li JS, Margossian R, Mital S, Russell J, Rhodes J, et al. A cross-sectional study of exercise performance during the first 2 decades of life after the Fontan operation. *J Am Coll Cardiol*. 2008;52:99–107. doi: 10.1016/j.jacc.2008.02.081
2. Goldberg DJ, Zak V, McCrindle BW, Ni H, Gongwer R, Rhodes J, Garofano RP, Kaltman JR, Lambert LM, Mahony L, et al. Pediatric heart network investigators. Exercise capacity and predictors of performance after Fontan: results from the pediatric heart network Fontan 3 study. *Pediatr Cardiol*. 2021;42:158–168. doi: 10.1007/s00246-020-02465-1
3. Avitabile CM, Leonard MB, Zemel BS, Brodsky JL, Lee D, Dodds K, Hayden-Rush C, Whitehead KK, Goldmuntz E, Paridon SM, et al. Lean mass deficits, vitamin D status and exercise capacity in children and young adults after Fontan palliation. *Heart*. 2014;100:1702–1707. doi: 10.1136/heartjnl-2014-305723
4. Avitabile CM, Goldberg DJ, Leonard MB, Wei ZA, Tang E, Paridon SM, Yoganathan AP, Fogel MA, Whitehead KK. Leg lean mass correlates with exercise systemic output in young Fontan patients. *Heart*. 2018;104:680–684. doi: 10.1136/heartjnl-2017-311661
5. Cordina RL, O'Meagher S, Karmali A, Rae CL, Liess C, Kemp GJ, Puranik R, Singh N, Celermajer DS. Resistance training improves cardiac output, exercise capacity and tolerance to positive airway pressure in Fontan physiology. *Int J Cardiol*. 2013;168:780–788. doi: 10.1016/j.ijcard.2012.10.012
6. Jacobsen RM, Ginde S, Mussatto K, Neubauer J, Earing M, Danduran M. Can a home-based cardiac physical activity program improve the physical function quality of life in children with Fontan circulation? *Congenit Heart Dis*. 2016;11:175–182. doi: 10.1111/chd.12330
7. Sutherland N, Jones B, Westcamp Aguero S, Melchiori T, du Plessis K, Konstantinov IE, Cheung MMH, d'Udekem Y. Home- and hospital-based exercise training programme after Fontan surgery. *Cardiol Young*. 2018;28:1299–1305. doi: 10.1017/S1047951118001166
8. Wittekind S, Mays W, Gerdes Y, Knecht S, Hambrook J, Border W, Jefferies JL. A novel mechanism for improved exercise performance in pediatric Fontan patients after cardiac rehabilitation. *Pediatr Cardiol*. 2018;39:1023–1030. doi: 10.1007/s00246-018-1854-3
9. Hedlund ER, Lundell B, Söderström L, Sjöberg G. Can endurance training improve physical capacity and quality of life in young Fontan patients? *Cardiol Young*. 2018;28:438–446. doi: 10.1017/S1047951117002360
10. Laohachai K, Winlaw D, Selvadurai H, Gnanappa GK, d'Udekem Y, Celermajer D, Ayer J. Inspiratory muscle training is associated with improved inspiratory muscle strength, resting cardiac output, and the ventilatory efficiency of exercise in patients with a Fontan circulation. *J Am Heart Assoc*. 2017;6:e005750. doi: 10.1161/JAHA.117.005750
11. Longmuir PE, Tyrrell PN, Corey M, Faulkner G, Russell JL, McCrindle BW. Home-based rehabilitation enhances daily physical activity and motor skill in children who have undergone the Fontan procedure. *Pediatr Cardiol*. 2013;34:1130–1151. doi: 10.1007/s00246-012-0618-8
12. Opocher F, Varnier M, Sanders SP, Tosoni A, Zaccaria M, Stellin G, Milanesi O. Effects of aerobic exercise training in children after the Fontan operation. *Am J Cardiol*. 2005;95:150–152. doi: 10.1016/j.amjcard.2004.08.085
13. Pyykkönen H, Rahkonen O, Ratia N, Lähteenmäki S, Tikkanen H, Piirilä P, Pitkänen-Argillander O. Exercise prescription enhances maximal oxygen uptake and anaerobic threshold in young single ventricle patients with Fontan circulation. *Pediatr Cardiol*. 2022;43:969–976. doi: 10.1007/s00246-021-02806-8
14. Turquetto ALR, Dos Santos MR, Agostinho DR, Sayegh ALC, de Souza FR, Amato LP, Barnabe MSR, de Oliveira PA, Liberato G, Binotto MA, et al. Aerobic exercise and inspiratory muscle training increase functional capacity in patients with univentricular physiology after Fontan operation: a randomized controlled trial. *Int J Cardiol*. 2021;330:50–58. doi: 10.1016/j.ijcard.2021.01.058
15. Brassard P, Poirier P, Martin J, Noël M, Nadreau E, Houde C, Cloutier A, Perron J, Jobin J. Impact of exercise training on muscle function and ergoreflex in Fontan patients: a pilot study. *Int J Cardiol*. 2006;107(1):85–94. doi: 10.1016/j.ijcard.2005.02.038
16. Morris NM, Udry JR. Validation of a self-administered instrument to assess stage of adolescent development. *J Youth Adolesc*. 1980;9:271–280. doi: 10.1007/BF02088471
17. Marino BS, Shera D, Wernovsky G, Tomlinson RS, Aguirre A, Gallagher M, Lee A, Cho CJ, Stern W, Davis L, et al. The development of the pediatric cardiac quality of life inventory: a quality of life measure for children and adolescents with heart disease. *Qual Life Res*. 2008;17:613–626. doi: 10.1007/s11136-008-9323-8
18. Crocker PR, Bailey DA, Faulkner RA, Kowalski KC, McGrath R. Measuring general levels of physical activity: preliminary evidence for the physical activity questionnaire for older children. *Med Sci Sports Exer*. 1997;29:1344–1349. doi: 10.1097/00005768-199710000-00011
19. Kowalski KC, Crocker PRE, Faulkner RA. Validation of a physical activity questionnaire for older children. *Pediatric Exercise Science*. 1997;9:174–186. doi: 10.1123/pes.9.2.174
20. Kowalski KC, Crocker PRE, Kowalski NP. Convergent validity of the physical activity questionnaire for adolescents. *Pediatric Exercise Science*. 1997;9:342–352. doi: 10.1123/pes.9.4.342

21. Oren A, Vos LE, Bos WJ, Safar ME, Uiterwaal CS, Gorissen WH, Grobbee DE, Bots ML. Gestational age and birth weight in relation to aortic stiffness in healthy young adults: two separate mechanisms? *Am J Hypertens*. 2003;16:76–79. doi: 10.1016/S0895-7061(02)03151-5
22. Urbina EM, Kimball T, Khoury PR, Daniels SR, Dolan LM. Increased arterial stiffness is found in adolescents with obesity or obesity-related type 2 diabetes mellitus. *J Hypertens*. 2010;28:1692–1698. doi: 10.1097/HJH.0b013e32833a6132
23. Burnham JM, Shults J, Semeao E, Foster BJ, Zemel BS, Stallings VA, Leonard MB. Body-composition alterations consistent with cachexia in children and young adults with Crohn disease. *Am J Clin Nutr.* 2005;82:413–420. doi: 10.1093/ajcn/82.2.413
24. Rowland T. *Pediatric Laboratory Testing: Clinical Guidelines*. Champaign, IL: Human Kinetics Publishers; 1992.
25. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting the anaerobic threshold by gas exchange. *J Appl Physiol*. 1986;60:2020–2027. doi: 10.1152/jappl.1986.60.6.2020
26. Burstein DS, McBride MG, Min J, Paridon AA, Perelman S, Huffman EM, O'Malley S, Del Grosso J, Groepenhoff H, Paridon SM, et al. Normative values for cardiopulmonary exercise stress testing using ramp cycle ergometry in children and adolescents. *J Pediatr*. 2021;229:61–69.e5. doi: 10.1016/j.jpeds.2020.09.018
27. Paridon SM, Alpert BS, Boas SR, Cabrera ME, Caldarera LL, Daniels SR, Kimball TR, Knilans TK, Nixon PA, Rhodes J, et al. Clinical stress testing in the pediatric age group: a statement from the American Heart Association Council on cardiovascular disease in the young, committee on atherosclerosis, hypertension, and obesity in youth. *Circulation*. 2006;113:1905–1920. doi: 10.1161/CIRCULATIONAHA.106.174375
28. Khiabani RH, Whitehead KK, Han D, Restrepo M, Tang E, Bethel J, Paridon SM, Fogel MA, Yoganathan AP. Exercise capacity in single-ventricle patients after Fontan correlates with haemodynamic energy loss in TCPC. *Heart.* 2015;101:139–143. doi: 10.1136/heartjnl-2014-306337
29. Lee VS, Resnick D, Bundy JM, Simonetti OP, Lee P, Weinreb JC. Cardiac function: MR evaluation in one breath hold with real-time true fast imaging with steady-state precession. *Radiology.* 2002;222:835–842. doi: 10.1148/radiol.2223011156
30. Kühl HP, Spuentrup E, Wall A, Franke A, Schröder J, Heussen N, Hanrath P, Günther RW, Buecker A. Assessment of myocardial function with interactive non-breath-hold real-time MR imaging: Comparison with echocardiography and breath-hold cine MR imaging. *Radiology*. 2004;231:198–207. doi: 10.1148/radiol.2311021237
31. Wei Z, Whitehead KK, Khiabani RH, Tree M, Tang E, Paridon SM, Fogel MA, Yoganathan AP. Respiratory effects on Fontan circulation during rest and exercise using real-time cardiac magnetic resonance imaging. *Ann Thorac Surg.* 2016;101:1818–1825. doi: 10.1016/j.athoracsur.2015.11.011
32. McBride MG, Binder TJ, Paridon SM. Safety and feasibility of inpatient exercise training in pediatric heart failure: a preliminary report. *J Cardiopulm Rehabil Prev*. 2007;27:219–222. doi: 10.1097/01.HCR.0000281766.59781.e8
33. Burstein DS, McBride MG, Rossano JW, O'Connor MJ, Lin KY, Mascio CE, White R, Iacobellis K, Rosenthal T, Paridon SM. Increasing pump speed during exercise training improves exercise capacity in children with ventricular assist devices. *ASAIO J*. 2021;67:449–456. doi: 10.1097/MAT.0000000000001231
34. Burstein DS, McBride MG, Edelson JB, Rossano JW, O'Connor MJ, Lin KY, Mascio CE, Paridon SM. Safety and feasibility of exercise rehabilitation in children with ventricular assist devices. *Pediatr Cardiol*. 2022;43:1029–1036. doi: 10.1007/s00246-022-02819-x
35. Ogden CL, Kuczmarski RJ, Flegal KM, Mei Z, Guo S, Wei R, Grummer-Strawn LM, Curtin LR, Roche AF, Johnson CL. Centers for Disease Control and Prevention 2000 growth charts for the United States: Improvements to the 1977 National Center for Health Statistics version. *Pediatrics*. 2002;109:45–60. doi: 10.1542/peds.109.1.45
36. Zemel BS, Kalkwarf HJ, Gilsanz V, Lappe JM, Oberfield S, Shepherd JA, Frederick MM, Huang X, Lu M, Mahboubi S, et al. Revised reference curves for bone mineral content and areal bone mineral density according to age and sex for black and non-black children: results of the bone mineral density in childhood study. *J Clin Endocrinol Metab.* 2011;96:3160–3169. doi: 10.1210/jc.2011-1111
37. Kalkwarf HJ, Zemel BS, Gilsanz V, Lappe JM, Horlick M, Oberfield S, Mahboubi S, Fan B, Frederick MM, Winer K, et al. The bone mineral density in childhood study: bone mineral content and density according to age, sex, and race. *J Clin Endocrinol Metab.* 2007;92:2087–2099. doi: 10.1210/jc.2006-2553
38. Zemel BS, Leonard MB, Kelly A, Lappe JM, Gilsanz V, Oberfield S, Mahboubi S, Shepherd JA, Hangartner TN, Frederick MM, et al. Height adjustment in assessing dual energy x-ray absorptiometry measurements of bone mass and density in children. *J Clin Endocrinol Metab*. 2010;95:1265–1273. doi: 10.1210/jc.2009-2057
39. Goldberg DJ, Zak V, Goldstein BH, McCrindle BW, Menon SC, Schumacher KR, Payne RM, Rhodes J, McHugh KE, Penny DJ, et al. Pediatric heart network investigators. Design and rationale of the Fontan Udenafil exercise longitudinal (FUEL) trial. *Am Heart J*. 2018;201:1–8. doi: 10.1016/j.ahj.2018.03.015
40. Goldberg DJ, Zak V, Goldstein BH, Schumacher KR, Rhodes J, Penny DJ, Petit CJ, Ginde S, Menon SC, Kim SH, et al. Pediatric heart network investigators. Results of the FUEL Trial. *Circulation*. 2020;141(8):641–651. doi: 10.1161/CIRCULATIONAHA.119.044352
41. Powell AW, Wittekind SG, Alsaied T, Lubert AM, Chin C, Veldtman GR, Cordina R, Katz DA, Mays WA, Knecht SK, et al. Body composition and exercise performance in youth with a Fontan circulation: a bio-impedance based study. *J Am Heart Assoc*. 2020;9:e018345. doi: 10.1161/JAHA.120.018345
42. Keteyian SJ, Patel M, Kraus WE, Brawner CA, McConnell TR, Piña IL, Leifer ES, Fleg JL, Blackburn G, Fonarow GC, et al. HF-ACTION investigators. Variables measured during cardiopulmonary exercise testing as predictors of mortality in chronic systolic heart failure. *J Am Coll Cardiol*. 2016;67:780–789. doi: 10.1016/j.jacc.2015.11.050
43. Rhodes J, Curran TJ, Camil L, Rabideau N, Fulton DR, Gauthier NS, Gauvreau K, Jenkins KJ. Impact of cardiac rehabilitation on the exercise function of children with serious congenital heart disease. *Pediatrics*. 2005;116:1339–1345. doi: 10.1542/peds.2004-2697
44. Dunton GF, Do B, Wang SD. Early effects of the COVID-19 pandemic on physical activity and sedentary behavior in children living in the U.S. *BMC Public Health.* 2020;20:1351. doi: 10.1186/s12889-020-09429-3
45. Martínez-Quintana E, Vega-Acedo LDC, Santana-Herrera D, Pérez-Acosta C, Medina-Gil JM, Muñoz-Díaz E, Rodríguez-González F. Mental well-being among patients with congenital heart disease and heart failure during the COVID-19 pandemic. *Am J Cardiovasc Dis.* 2021;11:618–623.
46. Gentili F, Cafiero G, Perrone MA, Bianco M, Salvati A, Giordano U, Silva Kikina S, Guccione P, De Zorzi A, Galletti L, et al. The effects of physical inactivity and exercise at home in young patients with congenital heart disease during the COVID-19 pandemic. *Int J Environ Res Public Health*. 2021;18:10065. doi: 10.3390/ijerph181910065
47. Hemphill NM, Kuan MTY, Harris KC. Reduced physical activity during COVID-19 pandemic in children with congenital heart disease. *Can J Cardiol*. 2020;36:1130–1134. doi: 10.1016/j.cjca.2020.04.038
48. Dirks S, Kramer P, Schleiger A, Speck HM, Wolfarth B, Thouet T, Berger F, Sallmon H, Ovroutski S. Home-based long-term physical endurance and inspiratory muscle training for children and adults with Fontan circulation-initial results from a prospective study. *Front Cardiovasc Med*. 2022;8:784648. doi: 10.3389/fcvm.2021.784648
49. Cahalin LP, Chase P, Arena R, Myers J, Bensimhon D, Peberdy MA, Ashley E, West E, Forman DE, Pinkstaff S, et al. A meta-analysis of the prognostic significance of cardiopulmonary exercise testing in patients with heart failure. *Heart Fail Rev*. 2013;18:79–94. doi: 10.1007/s10741-012-9332-0