

Original Article

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Impaired knee extension muscle strength in adolescents but not in children with Fontan circulation

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Abstract

Introduction: Impaired isometric muscle strength was previously reported in adults with Fontan circulation. However, it is unclear if this impairment is present in children and adolescents with Fontan circulation. We investigated isometric muscle strength of the lower limb in patients (6–18 years) with Fontan circulation in comparison with healthy controls. **Method:** In this cross-sectional study, 43 patients (6–18 years) with Fontan circulation and 43 age- and sex-matched controls were included. Isometric knee extension and plantar flexion muscle strength were assessed using dynamometry (Newton, N). Lean mass of the legs was assessed with dual-energy X-ray absorptiometry. Analyses were performed on group level ($n = 43$), and for subgroups that included children aged 6–12 years ($n = 18$) and adolescents aged 13–18 years ($n = 25$). **Results:** On group level, the patients with Fontan circulation had impaired isometric knee extension strength in comparison with the controls ($p = 0.03$). In subgroup analyses, impaired isometric knee extension strength was present in the adolescents ($p = 0.009$) but not in the children groups. For plantar flexion, there was no difference between patients and controls. There was no difference in lean mass between patients and controls (9.6 ± 4.3 kg vs. 10.8 ± 5.6 kg, $p = 0.31$). However, the lean mass was highly correlated to isometric knee extension strength (patients $r = 0.89$, controls $r = 0.96$, $p < 0.001$) and isometric plantar flexion strength (patients $r = 0.7$, controls $r = 0.81$, $p < 0.001$). **Conclusion:** The finding of impaired isometric knee extension muscle strength in adolescents (13–18 years) with Fontan circulation and no corresponding impairment in the children group (6–12 years) could imply that isometric muscle strength gets more impaired with age.

Impaired isometric muscle strength has been reported in adults with different CHDs, as well as within the specific subgroup of patients with Fontan circulation.^{1–3} Only a few studies have assessed isometric muscle strength in children and adolescents with CHD. Fricke et al reported lower grip strength in a group of 29 adolescent patients (14–23 years) with different complex heart lesions.⁴ Holm et al showed that motor competence as well as grip- and quadriceps strength was impaired in a group of 120 children (7–12 years) with different complex lesions.⁵ Patients with Fontan circulation are dependent on the skeletal muscle pump for venous return due to the absence of a sub-pulmonary ventricle.⁶ Further, the clinical experience is that patients with Fontan circulation often report of aching in the legs similar to that of growing pains. Also, commonly noticed in the clinical setting is thin legs, which could indicate muscle dysfunction. One study on children with Fontan circulation showed a lower functional upper-body strength, for example, ability to perform push-ups and sit-ups compared to healthy controls.⁷ However, another study recently reported that there was no difference in grip strength between children with Fontan circulation (6–12 years) and reference data.⁸ Overall, the knowledge about lower limb isometric muscle strength in children and adolescents with Fontan circulation is scarce. Therefore, the aim of the present study was to determine the extent of difference in the isometric muscle strength of the lower limbs in children and adolescents with Fontan circulation in comparison to age- and sex-matched controls. We hypothesised that lower limb isometric muscle strength is impaired in children and adolescents with Fontan circulation.

Methods**Study population**

Forty-three patients with Fontan circulation were tested between September 2017 and October 2018. These included 24 patients from the Stockholm region – Centre 1 and 19 patients from the

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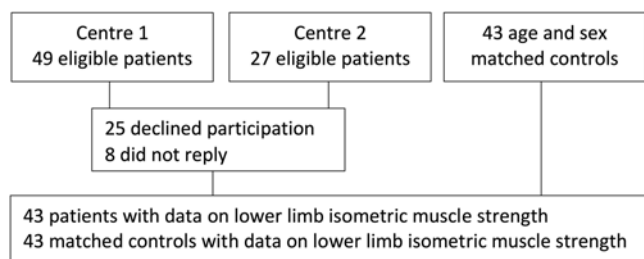


Figure 1. Flow chart over inclusion and exclusion processes.

northern health care region in Sweden – Centre 2 (Västerbotten, Norrbotten and Västernorrland). The patients were identified in the local registries of patients with Fontan circulation at the respective paediatric cardiology departments. Inclusion criteria were patients with Fontan circulation who were 6–18 years of age. The lower age limit was set to be 6 years of age or older since the test procedure was considered too complex for children younger than 6 years. Exclusion criteria were disabilities affecting performance of the muscle function tests (e.g. Down syndrome). Initially, 49 patients in the Stockholm region (Centre 1) and 27 patients in the northern health care region (Centre 2) were identified to fulfil the inclusion criteria. Information about the study was sent by surface mail to the patients and their parents. The parents were then contacted by telephone a few weeks later and asked about their children's participation. Of the 76 eligible patients who were contacted, 8 did not answer the phone and 25 declined participation due to medical reasons, fear of hospitals or lack of time/interest. This resulted in 43 patients who took part in the study (Fig 1).

For each patient, an age- and sex-matched control subject was recruited. The control subjects were assessed by echocardiography to exclude heart disease. The controls were recruited by convenience sampling, that is, from the population near the main study centre (Fig 1). The number of controls that declined participation was not registered.

Data about the patient's specific diagnosis were extracted from the SWEDish register on CONgenital heart disease.⁹ Height and weight were registered during the clinic visit for study participation. The body mass index was calculated using the paediatric z-score for patients between 5 and 19 years of age to describe relative weight adjusted to age and sex.¹⁰ The patients with Fontan circulation who participated in the study did not differ regarding age, sex, weight, height, body mass index, body mass index z-score¹⁰ or calf circumference compared to the age- and sex-matched controls (Table 1).

A *post hoc* analysis that included the 33 patients who did not reply or otherwise declined study participation showed no differences in age or sex compared to the 43 patients who participated in the study (age, 12.8 ± 3.4 years vs. 12.2 ± 3.9 years, $p = 0.5$; sex, male: $n = 16$ [48.5%] vs. $n = 25$ [58.1%], female: $n = 17$ [51.5%] vs. $n = 18$ [41.9%], $p = 0.4$).

For the participants under 18 years of age, both parents signed the consent form. Participants older than 15 years of age also gave their oral consent before initiating the muscle function tests, and those 18 years of age provided written informed consent themselves. The study conformed with the principles outlined by the declaration of Helsinki¹¹ and was approved by the regional Ethics Review Board, Umeå, Sweden (Dnr: 2016-445-31M).

Table 1. Descriptive data of children and adolescents with Fontan circulation and age- and sex-matched controls

	Patients (n = 43)	Controls (n = 43)	p-value
Age (years)	12.2 ± 3.9	12.3 ± 4.0	0.91
Sex			
Male	24 (56)	24 (56)	1.0
Female	19 (44)	19 (44)	
Weight (kg)	44.6 ± 18.4	45.7 ± 19.3	0.75
Weight (z-score)	-0.04 ± 1.0	0.04 ± 1.0	0.75
Height (cm)	149.8 ± 20.3	154.2 ± 22.3	0.35
Height (z-score)	-0.1 ± 1.0	0.1 ± 1.1	0.35
BMI (kg/m ²)	18.9 ± 3.6	18.3 ± 3.3	0.47
BMI (z-score)	0.1 ± 1.1	0.09 ± 1.0	0.40
Calf circumference (cm)	29.4 ± 4.9	30.4 ± 4.8	0.36
Systemic ventricle			
Left	24 (56)	na	
Right	19 (44)		
Oxygen StO ₂ %			
Pre-muscle test	93.7 ± 2.7	98.2 ± 1.1	<0.001
Post-muscle test	93.7 ± 2.5	98.1 ± 1.1	<0.001

BMI, body mass index; na, not applicable; StO₂, peripheral capillary oxygen saturation. Data are presented as the mean \pm standard deviation and n (%). Data on height and weight were missing in one of the controls. BMI z-score calculated for patients 5–19 years of age. Comparisons between patients and controls were performed using Students t-test and χ^2 test. Bold figures indicate p-values <0.05.

Isometric knee extension strength

Peak isometric muscle strength of the knee extensors was assessed using dynamometry (Anyload VETEK 0-5000 N; VETEK, Fioarno, Italy). For this test, participants sat on a gurney with back support and with 90 degrees flexion in hip and knee. A strap was connected to the dynamometer on one end and to an ankle cuff on the other end attached around the ankle (Supplementary Figure S1). Participants were instructed on command to perform a maximum knee extension and to hold the contraction for 5 s.

Isometric plantar flexion muscle strength

Peak isometric muscle strength of the plantar flexors of the ankle was assessed using the same dynamometer as described above. During this test, participants sat in a standardised position on a gurney with the test leg resting on the gurney with the knee in a straight position and with the angle of the ankle positioned at 90° flexion. The foot of the opposite leg was positioned on the floor or on a footrest, and the knee was at approximately 90° of flexion. The dynamometer was positioned resting on the knee and was attached with straps around the waist and under the foot. The foot strap was placed over the metatarsophalangeal joint. Participants wore a cast shoe to prevent the straps from moving, and a padded plank was placed behind the back to prevent the straps from being uncomfortable when performing the test (Supplementary Figure S2). Participants were instructed on command to press the foot towards the strap (plantar flexion) as hard as possible for 5 s.

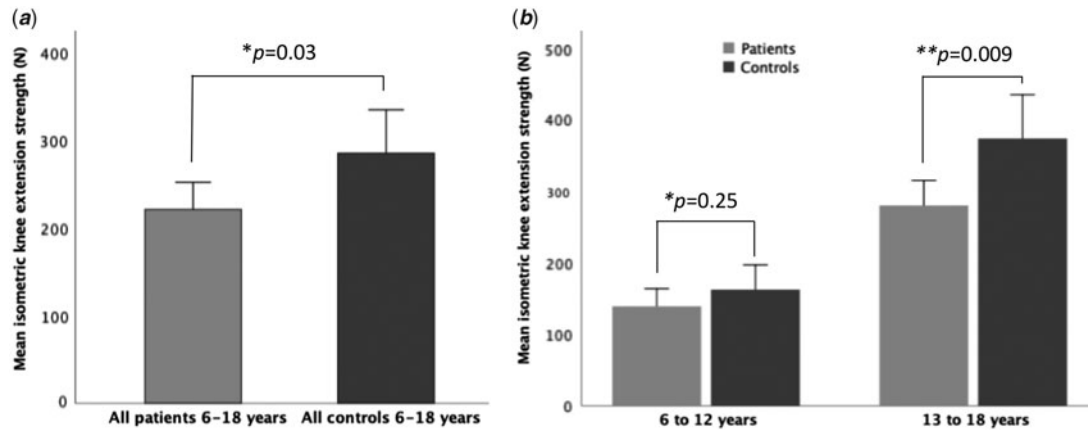


Figure 2. (a) Comparison of the isometric knee extension muscle strength test (N) in children and adolescents with Fontan circulation (6–18 years, $n = 43$) and age- and sex-matched controls ($n = 43$). (b) Subgroup comparison of the isometric knee extension muscle strength test (N) between children (6–12 years, $n = 18$) and adolescents (13–18 years, $n = 25$) with Fontan circulation and their respective controls. Data are presented as the mean with 95% confidence interval. N, Newton. Comparisons between patients and controls were performed using Students t-test. * p -values < 0.05 ; ** p -values < 0.01 .

After application of the test equipment and prior to initiating the first series of the isometric muscle tests, participants performed two to three submaximal muscle contractions in order to familiarise with the test procedure and the equipment. These submaximal muscle contractions were also considered as warm up. For each of the isometric muscle strength tests, three repeated measurements were performed with a 1-minute rest period between measurements. The mean peak force for all measurements of both legs for each respective strength test was used for statistical analyses. The investigator provided verbal guidance for when to start the contraction (three-two-one-go), encouragement during the entire contraction and when participants should stop. The tests were performed bilaterally, and with the order of which leg was tested first randomly assigned. The participants continuously got visual feedback regarding the force achieved from the monitor of the dynamometer.

Additional descriptive data

The calf circumference was measured at the largest girth using a tape measure, for each leg and a mean of both calves was used as a representative value for each participant. The finger arterial oxygen saturation (StO₂%) was assessed using a handheld pulse oximeter (GE Datex Ohmeda Tuffsat Handheld Pulse Oximeter; GE Healthcare, Stockholm, Sweden) (Table 1). This was performed both prior to and after the muscle tests.

Lean mass of legs

Full and regional body composition was assessed with dual-energy X-ray absorptiometry (Lunar iDXA, General Electric Healthcare, Madison, Wisconsin, United States of America). Lean body mass refers to the total body weight minus bone and fat, thus representing the skeletal muscle mass. In the present report, only data on the total lean mass of the legs are presented. Data on lean mass were present in 42 patients and 30 controls.

Physical activity

The amount of physical activity for each participant was assessed using a questionnaire included in SWEDish register on CONgenital heart disease. The younger children received help from their parents to answer the questionnaire. The questionnaire

comprised, for example, questions about participation in school sports and free time sports.⁹

Statistics

Statistical analyses were performed using the Statistical Package for Social Sciences version 25 (SPSS; IBM Corp., Armonk, New York, United States of America). All data are presented as means with standard deviations and ratios with percentages. Comparisons between patients and controls were analysed using Students t-test (means) and χ^2 test (ratios). Correlation analysis between lean mass of legs and isometric muscle strength was performed with Pearson correlation analysis. When significance was found on the group level, the data were divided into two subgroups that represented children (aged 6–12 years) and adolescents (aged 13–18 years). The choice of cut points for stratification by age was due to the significant physiological development of muscle function during puberty.^{12–14} Z-scores were calculated for height and weight. Cohen's d was used to calculate the effect size of the muscle strength tests. The null hypothesis was rejected for p -values < 0.05 .

Results

Isometric knee extension muscle strength

The patients with Fontan circulation had significantly lower isometric knee extension muscle strength compared to the controls ($p = 0.03$) (Fig 2a). The effect size on group level was -0.5 standard deviation. In the subgroup analysis, a significantly lower isometric knee extension muscle strength was found for the adolescent group (aged 13–18) ($p = 0.009$), but not for the children group (aged 6–12) ($p = 0.25$) (Fig 2b). The effect size for the adolescent group was -0.7 standard deviation and for the children was -0.2 standard deviation.

Isometric plantar flexion muscle strength

No differences were found on group level between patients and controls regarding isometric muscle strength of the plantar flexors (Fig 3a, b). The effect size on group level was -0.4 standard deviation, -0.5 standard deviation in the adolescent group and -0.3 standard deviation in the children group.

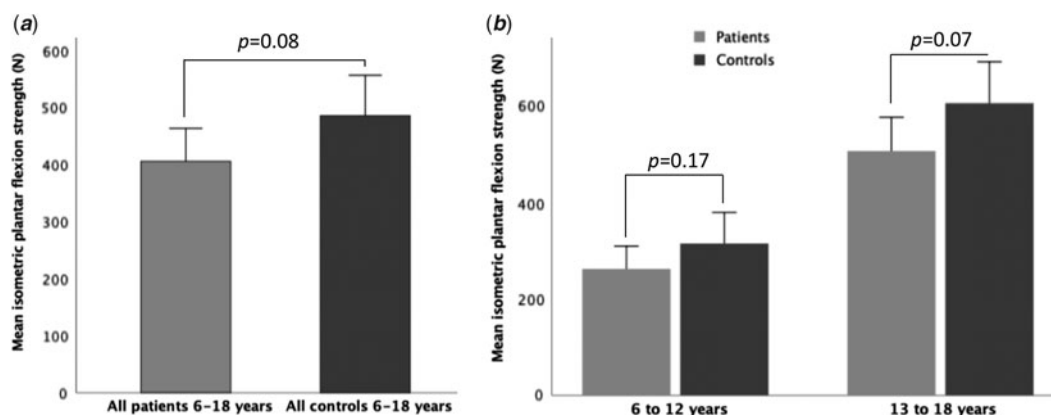


Figure 3 (a) Comparison of the isometric plantar flexion muscle strength test (N) in children and adolescents (6–18 years, $n = 43$) with Fontan circulation and age- and sex-matched controls ($n = 43$). (b) Subgroup comparison of the isometric plantar flexion muscle strength test (N) between children (6–12 years, $n = 18$) and adolescents (13–18 years, $n = 25$) with Fontan circulation and their respective controls. Data are presented as the mean with 95% confidence interval. N, Newton. Comparisons between patients and controls were performed using Students t-test.

Oxygen saturation

The peripheral capillary oxygen saturation was lower in patients with Fontan circulation both pre- and post- muscle-strength test procedures (Table 1).

Lean mass of legs

There was no difference in lean mass of legs between patients and controls (9.6 ± 4.3 kg vs. 10.8 ± 5.6 g, $p = 0.3$). Further, there was no difference in indexed lean mass of legs between patients and controls (4.0 ± 0.9 vs. 4.2 ± 1.0 kg/m², $p = 0.3$). The isometric muscle strength, in both patients and controls, was highly correlated to the lean mass of the legs both for isometric knee extension strength (patients $r = 0.89$, controls $r = 0.96$, $p < 0.001$) and for isometric plantar flexion strength (patients $r = 0.7$, controls $r = 0.81$, $p < 0.001$).

Physical activity

Fewer patients with Fontan circulation than controls reported participation in free time sport activities ($n[\%]$ patients 26[60.5] vs. controls 40[97.5], $p = 0.01$). However, no difference between groups was found regarding participation in school sports (data not shown).

Discussion

The main finding of the present study was that the isometric knee extension muscle strength was impaired in young patients with Fontan circulation (6–18 years) which was in line with our hypothesis. Further, a subgroup analysis showed that the isometric knee extension muscle strength was only impaired in adolescents (13–18 years) but not in the younger children (6–12 years) with Fontan circulation when compared to their respective controls. However, no differences were found on group level between patients and controls regarding isometric muscle strength of the plantar flexors. Therefore, our hypothesis of a more generalised muscle weakness of the lower limbs was not fully supported.

Impaired isometric knee extension muscle strength in adolescents (13–18 years), but not in children (6–12 years) with Fontan circulation, has not been reported previously. Previous studies on muscle strength in young patients with complex CHD are few and inconsistent,^{4,5,8} but the general consensus is that

there is impairment in peripheral muscle strength. Fricke et al reported on reduced grip strength in patients aged 14–23 years with different complex congenital heart lesions,⁴ and Hock et al. showed that children and adolescents with Fontan circulation have impaired functional upper-body muscle strength.⁷ Added together this could indicate that the Fontan patients, like other CHD, have a general impaired muscle strength. Somewhat surprisingly, we found no difference in knee extension muscle strength in children (6–12 years) with Fontan circulation and controls. However, this finding corresponds with a previous report by Longmuir et al on grip strength in a population with Fontan circulation; these authors also found no reduction in isometric strength in this age group.⁸ In contrast, a previous report showed impaired grip strength in children (aged 7–12) with different complex heart lesions.⁵ However, in the latter study, a mixture of different complex lesions and the use of an existing reference database for comparison may have affected the results. In the present study, we included age- and sex-matched controls for comparison. Additionally, we focused on lower limb muscle strength, which may complicate the comparison with the previous report that used grip strength and upper-body muscle function.^{4,5,7,8}

Although no statistically significant differences were found for isometric plantar flexion muscle strength, on average the results were similar between patients and controls (a tendency for significance, $p = 0.08$) as for the isometric knee extension strength. This pertains as well to the children (6–12 years) ($p = 0.17$) and adolescents (13–18 years) ($p = 0.07$) in comparison with respective controls with the same pattern as the isometric knee extension strength. It is possible that our study population might have been slightly underpowered regarding this specific test. It could only be speculated that a larger sample could have resulted in significance.

To provide inference of clinical significance, we calculated effect sizes on group and on subgroup levels. These calculations showed clinically important differences since the effect size for the knee extension strength on group level was moderate ($d = -0.5$) and for the adolescent subgroup trended towards large ($d = -0.7$). Despite the non-significant differences in plantar flexion strength, the effect size for the adolescent group was moderate, albeit small on group level. This may support the probability of an underpowered sample size regarding the plantar flexion test.

The present results regarding the impaired muscle strength in adolescents with Fontan circulation comply with the impaired

isometric knee extension muscle strength recently reported in adults with different complex heart lesions¹⁵ and previous data on impaired grip strength and respiratory muscle strength in adults with CHD.^{1–3} It is currently not known if this impairment is already present in early childhood, or if it develops with age. Yet with the present and previous reports at hand, it is tempting to speculate that the isometric muscle strength gets more impaired with increasing age. In order to better target development of muscle strength over time, the inclusion of repeated testing with ageing should be promoted in future research protocols.

The underlying mechanisms for the impaired isometric knee extension muscle strength in adolescents and adults with Fontan circulation are currently unknown. It could be speculated that the development of increased lean muscle mass and muscle strength, due to hormonal factors, might be inhibited in patients with Fontan circulation, which in turn could impact the muscle strength in this population. However, in the present study, we found differences regarding muscle strength but no differences regarding lean mass of the legs. However, it should be noted that the lean mass and muscle strength were highly correlated in both patients and controls. This could indicate that decline in muscle mass occurs slower than muscle strength and becomes visible first in adulthood. In contrast to our results on lean mass, there are previous reports on reduced lean mass in adults^{1,15} as well as in children with Fontan circulation.¹⁶ Taken together, this stresses the need of future research regarding underlying mechanisms and development of muscle strength and lean mass over time.

It has been stated that the majority of the clinical and physiological alignments in patients with Fontan circulation is caused by upstream venous congestion and downstream decreased output. Due to the lack of sub-pulmonary ventricle, the patients with Fontan circulation are dependent on the skeletal muscle pump and the ventilatory pump for venous return.⁶ The primary explanation for the reduced aerobic exercise capacity in patients with Fontan circulation has been, until recently, limited cardiorespiratory function. However, several studies suggest the skeletal muscle function as an important component for exercise capacity.^{2,7,17} The finding of impaired lower limb muscle function in adolescents and adults with Fontan circulation may therefore be an important contributing factor to the reduced exercise capacity that is seen in adulthood in these patients.^{18,19} Also, an exercise training protocol targeting skeletal muscle function was recently shown to increase the exercise capacity in adults with Fontan circulation. However, additional confirmative research is needed.

The impaired isometric muscle strength in the adolescents with Fontan circulation can partly be explained by physiological factors, although environmental factors may also contribute. It has been reported that parenting stress increases significantly when having children with complex CHD.²⁰ The potentially protective behaviour of the parents might affect the children's amount of physical activity from an early age. However, there are a limited number of studies that have investigated physical activity level in children with Fontan circulation.²¹ The majority of children and adolescents in the present study, both controls and those with Fontan circulation, were participating in school sports. However, the children and adolescents with Fontan circulation were less active in free time sport activities. The physical activity level of the present study population may have influenced the results of the isometric muscle strength tests. However, no objective measurement of physical activity was included in the study protocol. As mentioned above, these patients are dependent on the skeletal muscle pump for venous return,⁶ and therefore, a physically active life style might

be particularly important for this population. Resistance muscle training in adults with Fontan circulation was reported to improve muscle mass, muscle strength and exercise capacity.²² Introducing resistance muscle training in early adolescence might be important in order to prevent further deterioration of muscle function with age; however, more research is needed in this area.

Limitations

Some of the patients who declined participation ($n = 25$) stated medical reasons and fear of hospitals as reasons for declining. This could possibly indicate that these patients were more affected by their heart disease. As a consequence, it could be speculated that they would have performed worse on the muscle function tests. However, the patients who declined participation or did not answer the phone did not differ in age and sex compared to those who were included in the study. In that aspect, the participating patients were representative for the Fontan population aged 6–18 years.

It is challenging to perform tests on children as young as 6 years of age due to limited development of motor skills. However, the test procedure was strictly standardised, and tests were customised to also suit the younger children. Further, the use of dynamometry to assess isometric knee extension muscle strength is considered as reliable and valid; therefore, the results are considered appropriate.^{23–25} A limitation is that the quality aspects of testing isometric muscle strength in plantar flexion with isokinetic dynamometry has not been evaluated previously for children with CHD. However, the test procedure was standardised and was properly performed by all participants according to our observation. Further, as stated earlier, it is possible that the study population might have been slightly underpowered regarding this specific test as indicated by the borderline significant results.

There is a recent report showing a higher prevalence of delayed puberty in adolescents with Fontan circulation.²⁶ This could imply that the adolescent group in our study had not reached the level of maturity comparable to the respective controls. Whether this had any impact on our findings cannot be ascertained because the study protocol did not include any data on sex maturity, for example, Tanner stage. Therefore, this limitation is acknowledged.

Conclusion

We showed that isometric knee extension muscle strength is impaired in adolescents (13–18 years) with Fontan circulation compared to controls. However, no corresponding difference was found in children (6–12 years). When added to previous reports on impaired muscle strength in adults with complex CHD, the present data imply that the isometric muscle strength may become more impaired with increasing age. Thus, this stresses the importance of monitoring the development of muscle function over time and to investigate the effect of rehabilitation targeting muscle strength in this population.

Supplementary Material. To view supplementary material for this article, please visit <https://doi.org/10.1017/S1047951120001675>

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Conflict of Interest. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the Helsinki Declaration of 1975, as revised in 2008, and was approved by the regional Ethics Review Board, Umeå, Sweden (Dnr: 2016-445-31M).

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