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Clinical Research

Slower Skeletal Muscle Oxygenation Kinetics in Adults With Complex Congenital Heart Disease

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ABSTRACT

Background: Adults with complex congenital heart disease (CHD) show reduced aerobic exercise capacity and impaired skeletal muscle function compared with healthy peers. Peripheral muscle factors are presumed to be important contributors to the aerobic capacity, but the mechanisms are poorly understood. The aim of the present study was to investigate differences between adults with CHD and controls in muscle oxygenation kinetics at rest, and during and after exercise.

Methods: Seventy-four patients with complex CHD (mean age 35.6 ± 14.3 years, female n = 22) were recruited. Seventy-four age- and sex-matched subjects were recruited as controls. Muscle oxygenation was successfully determined on the anterior portion of the deltoid muscle using near-infrared spectroscopy in 65 patients and 71 controls. Measurements were made at rest, during isotonic shoulder flexions (0-90°) to exhaustion, and during recovery.

RÉSUMÉ

Contexte : Comparés à leurs pairs en santé, les adultes présentant une cardiopathie congénitale complexe ont une capacité d'effort aérobie réduite et une fonction musculosquelettique amoindrie. Les facteurs périphériques musculaires sont considérés comme jouant un rôle important dans la capacité aérobie, mais les mécanismes de leur influence sont mal connus. Notre étude visait à examiner les différences entre des adultes présentant une cardiopathie congénitale et des sujets témoins sur le plan de la cinétique d'oxygénation des muscles au repos, durant l'effort et après l'effort.

Méthodologie : Soixante-quatorze patients présentant une cardiopathie congénitale complexe (âge moyen : 35,6 ± 14,3 ans, nombre de femmes : 22) ont été recrutés, et 74 autres participants d'âge et de sexe correspondants ont été admis comme sujets témoins. L'oxygénation des muscles a pu être mesurée par spectroscopie dans

Adults with congenital heart disease have a reduced aerobic exercise capacity with a more pronounced reduction in patients with increased complexity of the heart lesion.[1] In addition, previous research has shown impaired skeletal muscle endurance capacity and isometric muscle strength in this population compared with healthy peers.[2-4] These peripheral muscle factors are presumed to be important contributors to the reduced aerobic exercise capacity.[5] The skeletal muscle endurance capacity (ie, the ability to perform repeated muscle contractions over time), is regulated by the delivery to and extraction of oxygen in the skeletal muscles during exercise.[6] In acquired heart failure, skeletal muscle endurance capacity is commonly impaired.[7,8] An important contributing factor to this phenomenon is the reduced cardiac output that results in diminished blood flow and oxygen delivery to skeletal muscles. Consequentially, the structural and functional capillary changes that occur in acquired heart failure lead to impaired oxygen kinetics in peripheral skeletal muscles that thereby affects muscle function.[9-11] Impaired peak aerobic exercise capacity is closely associated with prolonged post exercise recovery in patients with heart failure[12,13] and also in patients with congenital heart disease.[14] In patients with heart failure, impaired oxygen delivery to and distribution within the skeletal muscles have been suggested as mechanisms that affect exercise performance and post exercise recovery.[10,15] While there are a number of similarities between

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Results: The patients with CHD performed fewer shoulder flexions (40 ± 17 vs 69 ± 40; $P < 0.001$), had lower muscle oxygen saturation (StO_2) at rest (58 ± 18% vs 69 ± 18%; $P < 0.001$), slower desaturation rate at exercise onset (−9.7 ± 5.9 vs −15.1 ± 6.5% $StO_2 \times 3.5$ s^{-1}, $P < 0.001$), and slower resaturation rate post exercise (4.0 ± 2.7 vs 5.4 ± 3.6% $StO_2 \times 3.5$ s^{-1}; $P = 0.009$) compared with the controls. **Conclusions:** In comparison with age- and sex-matched controls, adults with complex CHD had slower oxygenation kinetics. This altered skeletal muscle metabolism might contribute to the impaired skeletal muscle endurance capacity shown and thereby also to the reduced aerobic capacity in this population.

Résultats : Les patients atteints de cardiopathie congénitale ont réussi à effectuer un moins grand nombre de flexions de l'épaule (40 ± 17 vs 69 ± 40; $p < 0,001$) et présentaient une saturation tissulaire musculaire en oxygène (StO_2) inférieure au repos (58 ± 18 % vs 69 ± 18 %; $p < 0,001$), un taux de désaturation plus lent à l'effort (StO_2 de -9,7 ± 5,9 vs -15,1 ± 6,5 % × 3,5 s^{-1}, $p < 0,001$) et un taux de resaturation plus lent après l'effort (StO_2 de 4,0 ± 2,7 vs 5,4 ± 3,6 % × 3,5 s^{-1}; $p = 0,009$) comparativement aux sujets témoins. **Conclusions :** Comparativement aux sujets témoins du même âge et du même sexe, les adultes atteints d'une cardiopathie congénitale complexe présentaient une cinétique d'oxygénation ralentie. Ce métabolisme altéré dans les muscles squelettiques pourrait contribuer à expliquer l'endurance musculaire réduite et donc la capacité aérobie amoindrie observée dans cette population.

patients with acquired heart failure and congenital heart disease, several distinct differences are apparent. Patients with acquired heart failure are elderly, more symptomatic, and have often acquired their disease late in life and the disease progression is relatively fast.[16] In contrast, adults with congenital heart disease are relatively young, and although surgically corrected or palliated, they are still affected by slightly altered physiology and hemodynamics throughout life[17]; this in turn might lead to the development of impaired skeletal muscle function.[2-4] Currently, the knowledge is scarce about peripheral muscle oxygenation kinetics in patients with congenital heart disease.

Near infrared spectroscopy (NIRS) is a noninvasive method for continuous monitoring of local muscle oxygenation (ie, the dynamic balance between oxygen delivery and consumption).[18] Using direct measurement of the ratio of oxygenated and deoxygenated hemoglobin within the muscle, NIRS is useful for providing information on oxygen consumption and recovery during exercise.[19-21] Previous studies using NIRS on patients with acquired heart failure concluded that these patients had impaired oxidative capacity[22] and a limitation in oxygen delivery and utilization (exhibited as slowed deoxygenation at exercise onset)[23] compared with controls. Although there are a number of studies that used NIRS on patients with acquired heart failure,[11,22,23] studies that used NIRS for patients with congenital heart disease are few. In one study, Moalla and coworkers reported that reduced muscle strength and endurance was associated with impaired muscle oxygenation kinetics for a small group of children (n = 9) with congenital heart disease that included simple and complex lesions.[21] Their conclusions were on the basis of patients that showed a greater magnitude of desaturation during exercise and a slower recovery post exercise than control subjects. Adults with congenital heart disease have passed the intense period of body development in puberty.[24] Furthermore, the effect of the heart lesion on skeletal muscle function probably progresses over time. To our knowledge, there are no reports on oxygenation kinetics in adults with congenital heart disease.

The aim of the present study was to investigate if muscle oxygenation kinetics differs between adults with complex congenital heart disease and age- and sex-matched controls. We hypothesized that desaturation at exercise onset and resaturation post exercise would be slower for adults with complex congenital heart disease compared with controls.

Methods

Patients and controls

In this multicentre cross-sectional study, 74 adults with complex congenital heart disease (mean age 35.6 ± 14.3 years, female n = 22) were recruited between March 2016 and December 2017 from 3 Swedish centres specialized in congenital heart disease in Umeå, Uppsala, and Lund (referred to as centre 1, centre 2, and centre 3, respectively). The inclusion criteria were adult age (> 18 years of age), clinically stable condition, and complex congenital heart disease.[25] The exclusion criteria were cognitive impairment affecting independent decision capacity, comorbidity (eg, rheumatoid arthritis) or other circumstances affecting study participation (eg, pregnancy). From centre 1, 91 patients were identified via the national register on congenital heart disease (**Swed**ish Registry of **Con**genital Heart Disease [SWEDCON]). Of these, 6 were excluded because of cognitive impairment, 14 were excluded because of comorbidity or other circumstances affecting study participation, 15 declined participation, and 5 were not possible to contact. Therefore, 51 patients (n = 15 women) were included from centre 1. From centre 2, a convenience sample of 22 patients (n = 11 women) was identified, and of these 11 patients (n = 6 women) declined participation. Therefore, 11 patients (n = 5 women) were included from centre 2. From centre 3, a convenience sample of 19 patients (n = 5 women) was identified, and of these 7 patients (n = 3 women) declined participation. Therefore, 12 patients (n = 2 women) were included from centre 3 (Fig. 1).

For each patient, an age- and sex-matched control was recruited. Controls should neither fulfil any of the previously mentioned exclusion criteria nor have a diagnosis of congenital heart disease. In this population-based recruitment of controls, stable conditions such as medically treated arterial

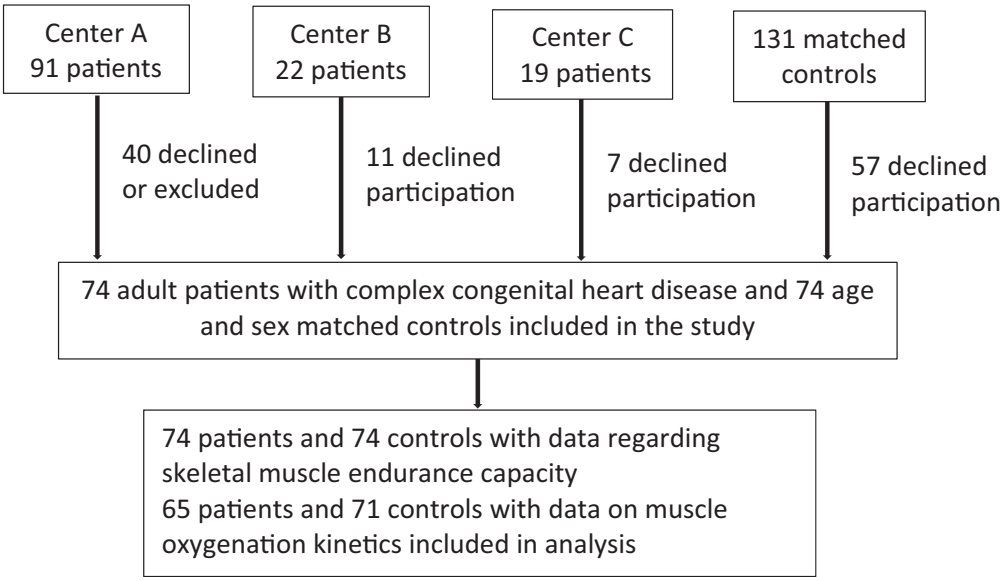

Figure 1. Flow chart of the inclusion and exclusion process of patients with complex congenital heart disease and age- and sex-matched controls.

hypertension were allowed. There were 131 persons identified via the national population register. These individuals were contacted via phone and asked for participation and 57 persons (44%; n = 19 women) declined or were not eligible for participation. In total, 74 persons were included as age- and sex-matched controls. In a post hoc analysis regarding age and sex between participating patients and those who declined or were excluded, no differences were found. Furthermore, no differences were found in the corresponding analysis in controls (data not shown).

Descriptive data of patients and controls are presented in Table 1. The patients were shorter, had lower arterial saturation at rest, and were prescribed more cardiovascular medication compared with controls (Table 1). Skeletal muscle endurance capacity was measured in all patients (n = 74) and controls (n = 74). Data on muscle oxygenation were successfully collected for 65 patients (n = 14 women) and 71 controls (n = 21 women; Fig. 1). Missing data were because of blunted response in NIRS signals in some subjects that might have been because of adipose tissue thickness.[26]

All members of the research team travelled to the different centres such that each respective procedure was performed by the same individual.

All participants gave their written informed consent for study participation. The study was approved by the Regional Ethical Review Board, Umeå (Dnr 2016-18-31M, 2016-462-32M, 2017-203-32M).

Arterial oxygen saturation

Before the exercise test, the arterial oxygen saturation (StO_2) was measured during rest on the index finger of the dominant hand using a Beurer PO 30 pulse oximeter (Beurer GmbH, Ulm, Germany).

Unilateral isotonic shoulder flexion

The unilateral isotonic shoulder flexion test (deltoid muscle activation) was used for assessment of muscle endurance capacity in the arm.[27] This test was chosen because it was used in previous research on adults with congenital heart disease and showed reduced endurance in patients compared with healthy controls.[3,4] The subject sat comfortably with the back touching the wall while holding a dumbbell, 2 kg for women and 3 kg for men, in the hand of the dominant side. Subjects were asked to elevate the arm from 0 to 90° flexion at a frequency of 20 repetitions (reps) per minute guided by a metronome (KORG metronome MA-30, KORG Inc, Tokyo, Japan) as many times as possible until they reached exhaustion. The test was aborted by the investigator if the participant was unable to follow the instructed pace or unable to reach 90° of flexion. The number of performed shoulder flexions was registered.[27]

NIRS

In the present study, the Inspectra 325 spectrometer (Hutchinson Technology, Hutchinson, MN) was used for NIRS measurements. The device is a continuous wave spectrometer capable of emitting and detecting light intensities at wavelengths of 680, 720, 760, and 800 nm. These wavelengths cover the spectrum that is sensitive for deoxyhemoglobin (HHb; lower wavelengths) and oxyhemoglobin (HbO_2; higher wavelengths). Second derivate spectroscopy applied to multiwavelength data (4 wavelengths) is used to remove baseline offset and linear slope from the optical density attenuation spectra.[28] The software for the device allows for absolute measurements of local tissue oxygenation in percent saturation, and relative measurements of HHb and HbO_2. In the present study, a 25-mm cylindrical probe was used that was equipped with a sender that emitted light at one tip and a photosensitive detector at the other tip. A signal from the muscle was obtained from a depth of 95% of the probe length (ie, up to 23 mm). The probe was placed over the anterior portion of the deltoid muscle with the upper rim of the probe positioned just beneath the posterior process of acromion and in direction of the muscle fibres of the dominant arm. An adhesive shield with a window was attached to

Table 1. Descriptive data for patients with complex congenital heart disease and age- and sex-matched controls

	Patients (n = 74)	Controls (n = 74)	*P*
Age, years	35.6 ± 14.3	35.7 ± 14.3	0.97
Sex			
Male	52 (70.3)	52 (70.3)	0.99
Female	22 (29.7)	22 (29.7)	
Height, cm	173.3 ± 9.6	176.8 ± 9.2	0.024*
Weight, kg	74.0 ± 12.1	76.6 ± 13.8	0.23
Arterial O_2 saturation, %	95 ± 4	98 ± 1	< 0.001†
NYHA classification			
I	49 (66.2)	na	Na
II	19 (25.7)		
III	3 (4.1)		
IV	0 (0)		
Extracardial physical limitation‡	3 (4.1)		
Diagnosis			
ToF	20 (27.0)	na	Na
PA	3 (4.1)		
ccTGA	4 (5.4)		
dTGA Senning/Mustard	15 (20.3)		
Fontan/TCPC	22 (29.7)		
Complete AV septal defect	1 (1.4)		
Miscellaneous	1 (1.4)		
Truncus arteriosus	1 (1.4)		
Eisenmenger	1 (1.4)		
dTGA ASO	6 (8.1)		
Surgical intervention, yes	70 (94.6)	na	Na
Age at intervention, years	5.5 ± 12.8	na	Na
Cardiovascular medication, yes	45 (60.8)	6 (8.1)	< 0.001†
ARB, yes	6 (8.1)	4 (5.4)	0.75
ACE-Is, yes	23 (31.1)	2 (2.7)	< 0.001†
β-Blockers, yes	23 (31.1)	0 (0)	< 0.001†
Calcium channel blockers, yes	4 (5.4)	2 (2.7)	0.68
Aldosterone blockers, yes	1 (1.4)	0 (0)	1.0
Diuretics, yes	13 (17.6)	1 (1.4)	0.001§
Warfarin, yes	17 (23.3)	0 (0)	< 0.001†
Aspirin, yes	13 (17.8)	0 (0)	< 0.001†
NOACs, yes	3 (4.1)	0 (0)	0.25
Statins, yes	4 (5.4)	1 (1.4)	0.36
PAH medication, yes	2 (2.7)	0 (0)	0.5
Amiodarone, yes	1 (1.4)	0 (0)	1.0
Nitroglycerine, yes	2 (2.7)	0 (0)	0.5
Digoxin, yes	2 (2.7)	0 (0)	0.5

Data are presented as mean ± 1 SD or n (%) except where otherwise noted. Comparisons between patients and controls were performed using Student *t* test (mean), χ^2(proportions), or Fischer exact test (used in comparison regarding the different cardiovascular medications). Bold figures denote *P* values < 0.05.

ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor II blocker; AV, arterioventricular; ccTGA, congenitally corrected transposition of the great arteries; dTGA ASO, transposition of the great arteries corrected with arterial switch operation; dTGA Senning/Mustard, transposition of the great arteries corrected with Senning/Mustard surgery; na, not applicable; NOAC, new oral anticoagulant; NYHA, New York Heart Association; PA, pulmonary atresia; PAH, pulmonary arterial hypertension; TCPC, total cavopulmonary connection; ToF, tetralogy of Fallot.

* $P < 0.05$.

† $P < 0.01$.

‡ Limited by joint-related problem while walking/running (n = 2), impaired balance post stroke (n = 1).

§ $P < 0.001$.

the skin to secure the probe. The shield was placed on the muscle by the same investigator for all subjects. NIRS signals were recorded at baseline, during isotonic shoulder flexions (0-90°) to exhaustion, and during 60 seconds of recovery (or until a recovery plateau was reached). NIRS measurements were sampled every 3.5 s into a portable computer. At the end of recording of a subject, the data were saved and exported in text format for offline processing using Microsoft Excel (Microsoft Corp, Redmond, WA).

A typical response during exercise was an abrupt decrease in signals for oxygen saturation percent and HbO_2, and an accompanying increase in HHb at the start, a plateauing of variables (for saturation percent this resulted in a plateau at 0% for patients and controls) with exercise continuation, and a trending recovery of components at the end of exercise (Fig. 2). The following variables were determined: muscle oxygen saturation at rest: a mean of the saturation percent for a 35-s rest period before exercise; desaturation rate: the slope of change of the saturation percent for the initial 15 s at the start of exercise; fractional oxygen extraction: change between the pre-exercise HHb value (mean for the 35-s rest before exercise) and the HHb mean value for a 10.5-s plateaued period during the exercise; resaturation rate: the slope of change of the saturation percent for the initial 25 s at the end of exercise; and half recovery time: time it took for the saturation percent to reach half of the peak hyperemic value post exercise. For the half recovery time calculation, an algorithm was applied to extrapolate the data to create a data point every

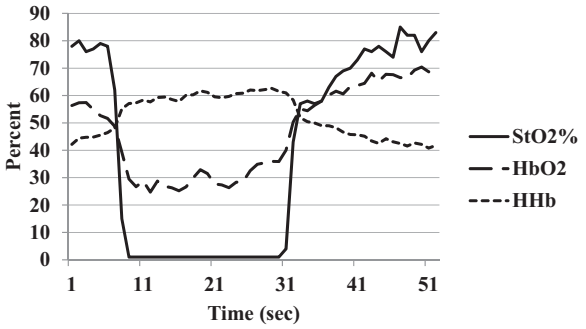

Figure 2. Typical curve for 1 subject showing responses in near infrared spectroscopy (NIRS) parameters before, during, and after exercise. HbO_2, oxyhemoglobin; HHb, deoxyhemoglobin; StO_2, oxygen saturation.

second, and the maximal data point post exercise was chosen as the peak hyperemic value.

International Physical Activity Questionnaire

Self-reported physical activity was assessed using the short version of the International Physical Activity Questionnaire (IPAQ). The IPAQ comprises 4 generic items regarding time spent at different intensity levels of physical activity and a summary (vigorous, moderate, walking, and total activity) in daily living during the past 7 days. This was summarized as a continuous score of metabolic equivalents (MET) minutes per week.[29]

Statistics

The statistical analyses were performed using the Statistical Package for Social Sciences version 24 (IBM Corp, Armonk, NY). All data are presented as mean, median, and ratio, with SD, range, and percentages, respectively. Differences between groups were analyzed using Student t test (mean), Mann-Whitney U test (median), and χ^2 test (ratio). Subgroup analysis was performed regarding differences between male patients and controls and female patients and controls. Further, subgroup analysis was performed regarding differences between controls and each of the 3 main diagnosis groups (ie, patients with tetralogy of Fallot [ToF]/pulmonary atresia [PA]; n = 23), patients with congenitally corrected transposition of the great arteries, and dextrotransposition of the great arteries corrected with atrial switch (ie, patients with systemic right ventricle [RV]; n = 19), and patients palliated with Fontan/total cavopulmonary connection (TCPC; n = 22). In the subgroup analysis, a comparison was made between a respective subgroup and the main group of controls. Student t test and Mann-Whitney U test were applied and yielded the same results. For multiple group comparisons in subgroup analyses, the Bonferroni correction was applied. To evaluate the association of age on oxygenation kinetics a univariate linear regression analysis was performed in the patient and control groups separately, with reoxygenation rate as the dependent variable and age as independent variable. The null hypothesis was rejected for P values < 0.05.

Results

Muscle endurance capacity

The patients performed fewer shoulder flexions compared with controls (40 ± 17 reps vs 69 ± 40 reps; $P < 0.001$; Table 2). The results persisted in analysis between male patients and controls as well as between female patients and controls (data not shown). Analysis of muscle endurance capacity in the 3 main diagnosis groups (ie, patients with ToF/PA [n = 23], patients with systemic RV [n = 19], and patients palliated with Fontan/TCPC [n = 22]) showed that all groups performed fewer shoulder flexions than controls (ToF/PA 38 ± 16 reps vs 69 ± 40 reps [$P < 0.001$], systemic RV 41 ± 14 reps vs 69 ± 40 reps [$P < 0.001$], Fontan/TCPC 35 ± 14 reps vs 69 ± 40 reps [$P < 0.001$]; Fig. 3A).

Muscle oxygenation at rest

The patients had a lower muscle oxygen saturation at rest compared with controls (58 ± 18% vs 69 ± 18%; $P < 0.001$; Table 2).

In the subgroup analysis of patients with ToF/PA and systemic RV, no differences in muscle oxygen saturation at rest was found compared with the controls (ToF/PA, 61 ± 19% vs 69 ± 18% [$P = 0.26$]; systemic RV, 58 ± 16% vs 69 ± 18% [$P = 0.06$]). In contrast, the patients palliated with Fontan/TCPC had a lower muscle oxygen saturation at rest than controls (53 ± 16% vs 69 ± 18%; $P < 0.003$; Fig. 3B).

Muscle oxygenation during exercise

The desaturation rate at exercise onset was slower in the patients compared with controls (−9.7 ± 5.9% $StO_2 \times 3.5$ s^{-1} vs −15.1 ± 6.5% $StO_2 \times 3.5$ s^{-1}; $P < 0.001$; Table 2).

Table 2. Comparison of skeletal muscle endurance capacity and muscle oxygenation variables of patients with complex congenital heart disease and age- and sex-matched control group

	Patients (n = 65)	Controls (n = 71)	P
Shoulder flexions, repetitions	40 ± 17	69 ± 40	**< 0.001***
Muscle oxygen saturation at rest, %	58 ± 18	69 ± 18	**< 0.001***
Desaturation rate, % $StO_2 \times 3.5$ s^{-1}	−9.7 ± 5.9	−15.1 ± 6.5	**< 0.001***
Fractional oxygen extraction, Δ%	4.7 ± 4.7	6.1 ± 4.8	0.09
Half recovery time, s	7.9 ± 6.8	7.1 ± 4.8	0.4
Resaturation rate, % $StO_2 \times 3.5$ s^{-1}	4.0 ± 2.7	5.4 ± 3.6	**0.009†**

Data are presented as mean ± 1 SD except where otherwise noted. Comparisons are between patients and controls using Student t test. Bold values denote P values < 0.05.

StO_2, oxygen saturation.

* $P < 0.05$.

† $P < 0.01$.

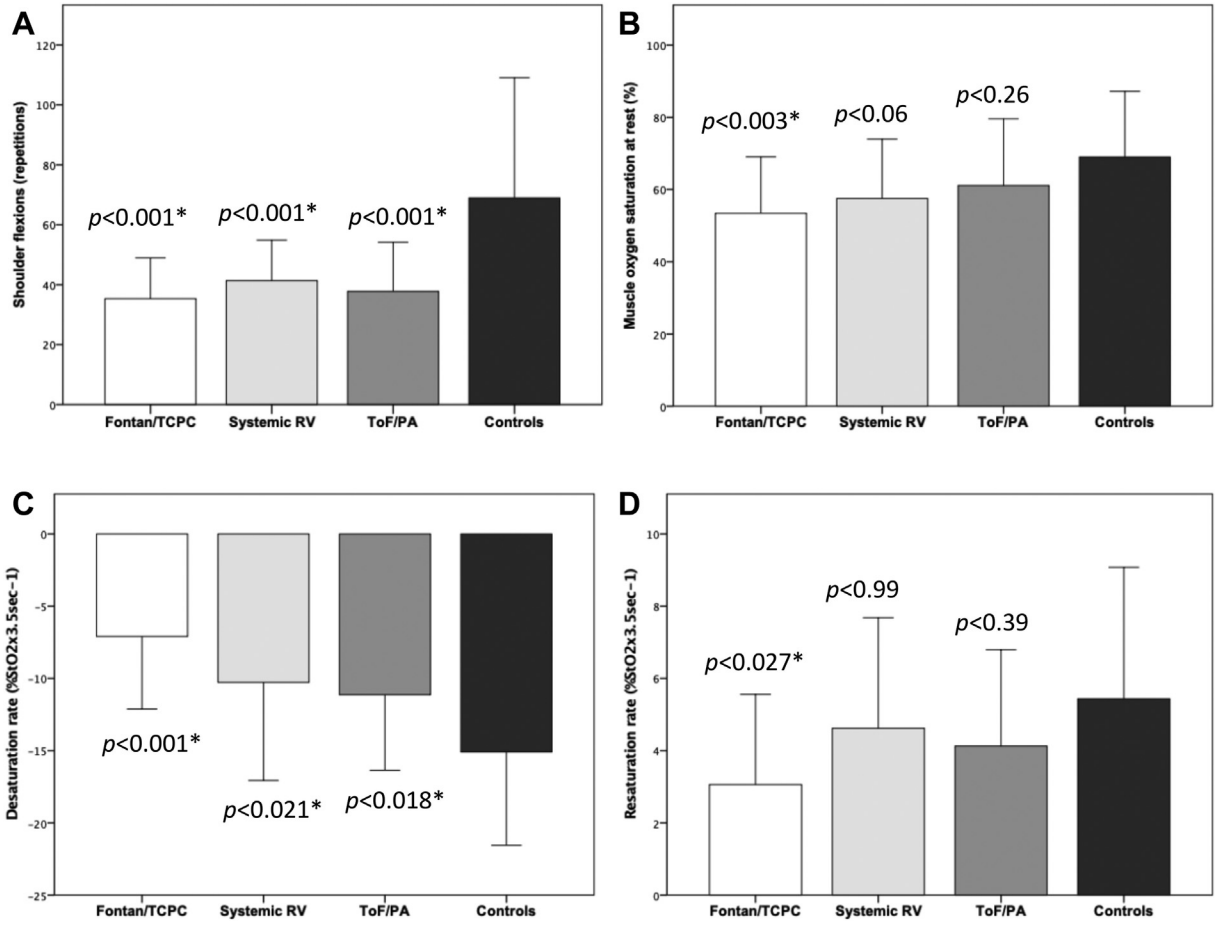

Figure 3. Comparison between the 3 diagnosis groups and the control group regarding (**A**) number of shoulder flexions performed (repetitions); (**B**) muscle oxygen saturation at rest (%); (**C**) desaturation rate at exercise onset (% $StO_2 \times 3.5\ s^{-1}$); and (**D**) resaturation rate post exercise (% $StO_2 \times 3.5\ s^{-1}$). **Bars** represent mean and **error bars** denote ± 1 SD. The *P* values denotes comparisons between subgroups of patients and controls. The *P* values are corrected for multiple comparisons using Bonferroni correction. * Denotes *P* values < 0.05. StO2, oxygen saturation; TCPC, total cavopulmonary connection; ToF, tetralogy of Fallot; PA, pulmonary atresia; RV, right ventricle.

In the subgroup analysis of patients with ToF/PA, systemic RV and patients palliated with Fontan/TCPC, slower desaturation rates at exercise onset were found compared with the control group (ToF/PA: $-11.1 \pm 5.2\%\ StO_2 \times 3.5\ s^{-1}$ vs $-15.1 \pm 6.5\%\ StO_2 \times 3.5\ s^{-1}$ [$P = 0.018$]; systemic RV: $-10.3 \pm 6.8\%\ StO_2 \times 3.5\ s^{-1}$ vs $-15.1 \pm 6.5\%\ StO_2 \times 3.5\ s^{-1}$ [$P = 0.021$]; Fontan/TCPC: $-7.1 \pm 5.0\%\ StO_2 \times 3.5\ s^{-1}$ vs $15.1 \pm 6.5\%\ StO_2 \times 3.5\ s^{-1}$ [$P < 0.001$]; Fig. 3C).

In analysis of the fractional oxygen extraction during exercise, no differences were found between the patients and the controls ($4.7 \pm 4.7\Delta\%$ vs $6.1 \pm 4.8\Delta\%$; $P = 0.09$; Table 2).

Muscle oxygen saturation after exercise

The patients had a slower resaturation rate post exercise ($4.0 \pm 2.7\%\ StO_2 \times 3.5\ s^{-1}$ vs $5.4 \pm 3.6\%\ StO_2 \times 3.5\ s^{-1}$; $P = 0.009$) compared with the controls. However, no difference was found regarding the half recovery time (7.9 ± 6.8 s vs 7.1 ± 4.8 s; $P = 0.4$; Table 2).

The subgroup analysis of recovery kinetics showed that patients with ToF/PA and systemic RV had resaturation rates post exercise that were not different than controls (ToF/PA, $4.1 \pm 2.7\%\ StO_2 \times 3.5\ s^{-1}$ vs $5.4 \pm 3.6\%\ StO_2 \times 3.5\ s^{-1}$ [$P = 0.39$]; systemic RV, $4.6 \pm 3.1\%\ StO_2 \times 3.5\ s^{-1}$ vs $5.4 \pm 3.6\%\ StO_2 \times 3.5\ s^{-1}$ [$P = 0.99$]), however, the patients with Fontan/TCPC had a slower resaturation rate post exercise than controls (Fontan/TCPC, $3.1 \pm 2.5\%\ StO_2 \times 3.5\ s^{-1}$ vs $5.4 \pm 3.6\%\ StO_2 \times 3.5\ s^{-1}$; $P = 0.027$; Fig. 3D).

Regression analysis

In the univariate linear regression analysis, age was independently associated with reoxygenation rate post exercise in patients but not in controls (patients, B = 0.07; 95% confidence interval, 0.02-0.12 [$P = 0.002$; $R^2 = 0.15$]; controls, B = −0.03; 95% confidence interval, −0.09 to 0.03 [$P = 0.26$; $R^2 = 0.02$]).

Self-reported physical activity

According to the IPAQ, the patients and controls reported their habitual physical activity as not different (2667 ± 2735 MET min/wk vs 2845 ± 2833 MET min/wk; $P = 0.7$).

Discussion

The main finding of this study was that adults with complex congenital heart disease had slower oxygenation kinetics than age- and sex-matched controls. Therefore, our hypothesis was confirmed. When separated into groups of lesion types, we found that it was only the group with Fontan physiology that had a slower resaturation rate than the controls. This altered skeletal muscle metabolism might contribute to the reduced aerobic capacity commonly found in this patient population.

Muscle oxygenation at rest

The lower muscle oxygen saturation at rest found in our population of patients with complex congenital heart disease has not been reported previously. In a similar type of study, no difference in baseline saturation levels was reported between children with congenital heart disease and controls.[21] Our finding complies with recently published data showing differences between patients with acquired heart failure and controls.[30] The muscle saturation level at rest might be a contributing factor in the endurance capacity. In a previous report on healthy athletes, it was shown that reduced arterial oxygen saturation was associated with impaired peripheral muscle performance.[31] Of note, our patients also had a lower finger arterial saturation than controls. However, a direct connection between this value and the muscle saturation is not straightforward because finger oximetry measures the arterial saturation and NIRS measures the balance between the arterioles and venules. When separated in subgroups, only the patients with Fontan/TCPC had lower muscle oxygen saturation at rest compared with the control group. This subgroup was also the only one that had a lower finger arterial oxygen saturation compared with controls (data not shown). Another study also reported a lower finger arterial oxygen saturation for children with Fontan/TCPC compared with controls.[32]

Muscle endurance and muscle oxygenation during exercise

In addition to the impaired muscle endurance capacity that has been reported for patients with congenital heart disease,[3,4] we found this to be consistent in men and women separately as well as in the subgroups with ToF/PA, systemic RV, and Fontan/TCPC.

Further, we found a slower desaturation rate at exercise onset for the patients. This complies with previous studies that described slower desaturation rates at the onset of exercise for children with congenital heart disease[21] and in adults with acquired heart failure.[23] A possible physiological explanation to the differences in desaturation rates could be limited blood flow to peripheral muscles as well as potential muscle dysfunction for the patients. As a comparison, patients with peripheral arterial disease exhibit impaired oxygen use at exercise onset presumably because of limited blood flow and oxygen delivery secondary to atherosclerotic arterial occlusion.[33] Also, in patients with heart failure, reduced cardiac output and impaired local muscle blood flow are stated as underlying mechanisms for impaired muscle function.[9-11] Acquired heart failure commonly affects older patients and the progression rate of the disease is relatively fast[16]; whereas adults with congenital heart disease, although surgically corrected, are affected by altered physiology and hemodynamics since early childhood, albeit at a modest grade. Patients with systemic RV generally have an impaired ability to increase cardiac output during exercise, which affects the oxygen delivery, and this might progress over time.[17] In patients palliated with Fontan/TCPC, the lack of a subpulmonary ventricle substantially limits the cardiac output during exercise.[34] Impaired cardiac output might influence the development of local muscle capillarization over time in patients with congenital heart disease, which is a phenomenon previously reported in patients with heart failure.[35] In contrast, patients with ToF (ie, patients with biventricular hearts who in general have rather high aerobic capacity[1]) still might have residual heart defects (eg, right ventricular outflow tract obstruction or pulmonary insufficiency) that might adversely affect cardiac function. As a consequence, a low grade of cardiac limitation might negatively affect the peripheral skeletal muscle function over time. The impaired muscle function found in the relatively young population in our study (approximately 36 years old) implies that it could be important to monitor the development over time, and rehabilitation targeting muscle function could be indicated to prevent further deterioration.

Although the patients had a lower oxygen saturation at baseline and a slower desaturation rate at exercise onset, the fractional oxygen extraction was not different than in controls. A rationale we had was that the prolonged reduction in cardiac output and the resulting underperfusion that is common in patients with congenital heart disease would, by adaptation, affect the level of oxygen extraction during exercise. However, this was not supported in our data. Therefore, because our patients and controls extracted the same relative magnitude of oxygen during exercise other factors are at play to account for the fewer reps performed by the patients. In a previous study in children with congenital heart disease a greater desaturation during exercise than in healthy controls was reported.[21] The previous authors used the decrease in oxygen saturation as an index of desaturation, whereas we used the increase in HHb. A reason for this was because our saturation signals plateaued at 0% for both groups rendering this variable not useful for desaturation determination. This point along with differences in exercise protocols might contribute to discrepancies between the previous study and our finding.

Muscle oxygenation after exercise

After exercise, the patients with congenital heart disease showed a slower resaturation rate than controls. However, when separated into subgroups, it was only the patients palliated with Fontan/TCPC who showed a slower oxygen resaturation rate. Compared with the other subgroups in our study, patients with Fontan/TCPC had a more limited circulatory capacity.[1] More specifically, this could be explained by the absence of a subpulmonary ventricle in Fontan physiology, which implies an impaired ability to increase cardiac output[34] and increased systemic venous pressure during exercise[32] that together might affect the rate of oxygen recovery. A possible mechanism explaining the decreased resaturation rate found in Fontan/TCPC, but not in ToF/PA and systemic RV, might be the damming effect of increased systemic venous pressure[34] that is unique for the Fontan circulation;

this can potentially reduce the outflow from the muscle after exercise.

For half recovery time, there was no difference between our patients and controls. This finding is in contrast to a previous study that showed a slower half recovery time for children with congenital heart disease compared with controls.[21] Conclusions of post exercise oxygenation recovery are often generalized between studies without regard to the type of variable assessed (ie, resaturation rate vs half recovery time). A presumption is that resaturation rate and half recovery time data are inter-related, but they actually express separate physiological entities. We chose to present data for both variables to get a fuller mechanistic picture of recovery for our patients. Half recovery time is anchored to the post-exercise hyperemic response, whereas resaturation rate calculations reflect the initial recovery at which primarily vascular components are restored (thus, is not influenced by the hyperemic response). Chance and coworkers stated that the rate of resaturation is related to the lactate accumulation during exercise.[36] Because this was not measured, differences in lactate accumulation during exercise between our patients and controls cannot be ascertained. This might be of interest for future studying. The lack of group difference in half recovery time could be because of differences in the absolute level of hyperemia between groups; however, this value was not measured in the present study.

Age was associated with recovery rate post exercise in patients, but not in the controls. A speculation is that muscle oxygen kinetics in healthy subjects is preserved to a higher extent during aging. In contrast, the recovery rate in patients is prolonged with age, presumably reflecting the slow deterioration of heart function over time.[5,17] This association is also in line with the relation between heart function and peripheral muscle function that was observed in patients with acquired heart failure.[35] Further, our finding is consistent with a previous report on heart failure showing that aging potentiated the effect of heart failure in muscle oxygenation.[37] Taken together, this underlines the potential importance of monitoring over time.

In the present study, we found no differences between patients and controls in self-reported physical activity level. This complies with previous reports[38,39] and implies that differences in physical activity level do not explain the differences we found in muscle oxygenation capacity between groups.

Limitations

A potential limitation of the present study is the subgroup sample size, which could have affected the subgroup comparisons. However, despite this, we identified possible underlying mechanisms for the reduced muscle endurance capacity. Another limitation of the present study was problems with the NIRS signals that might have been related to adipose tissue thickness that caused some missing data (patients n = 9, controls n = 3). Adipose tissue thickness is a known problem with NIRS.[26] However, the number of patients with complete data (n = 65) still provides robust data for overall analysis. A further limitation is the cross-sectional study design that does not provide information regarding the development of muscle function over time. Future study protocols should include repeated measurements to investigate this. Additionally, the study protocol did not include assessment of cardiopulmonary capacity. However, there is a known association between muscle function and aerobic capacity.[2]

Conclusion

Compared with age- and sex-matched controls, adults with complex congenital heart disease had slower oxygenation kinetics. This altered skeletal muscle metabolism might contribute to the impaired skeletal muscle endurance capacity that we show, and thereby also to the reduced aerobic capacity commonly found in this population. Because our group of patients was rather young, our findings might imply that monitoring muscle function over time could be of importance to detect deterioration. Further, we warrant investigation of the effect of exercise training on skeletal muscle function.

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Disclosures

The authors have no conflicts of interest to disclose.

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