International Journal of Cardiology 296 (2019) 57–62

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Sarcopenia is common in adults with complex congenital heart disease

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ARTICLE INFO

Article history:
Received 14 February 2019
Received in revised form
7 May 2019
Accepted 6 June 2019

Keywords:
Adult congenital heart disease
Complex congenital heart disease
DXA
Dual-energy x-ray absorptiometry
Sarcopenia

ABSTRACT

Background: Adults with complex congenital heart disease (CHD) have reduced aerobic capacity and impaired muscle function. We therefore hypothesized that patients have a lower skeletal muscle mass and higher fat mass than controls.

Methods: Body composition was examined with full body Dual-Energy x-ray Absorptiometry (DXA) in 73 patients with complex CHD (mean age 35.8 ± 14.3, women $n = 22$) and 73 age and sex matched controls. Patients fulfilling criteria for low skeletal muscle mass in relation to their height and fat mass were defined as sarcopenic.

Results: Male patients ($n = 51$) were shorter (177.4 ± 6.6 cm *vs.* 180.9 ± 6.7 cm, $p = 0.009$) and weighed less (76.0 ± 10.8 kg *vs.* 82.0 ± 12.4 kg, $p = 0.01$) than controls. Also, patients had a lower appendicular lean mass-index (ALM-index) (7.57 ± 0.97 kg/m^2 *vs.* 8.46 ± 0.90 kg/m^2, $p < 0.001$). Patients' relative tissue fat mass (27.9 ± 7.0% *vs.* 25.4 ± 8.6%, $p = 0.1$) did not differ. Forty-seven percent of the men ($n = 24$) were classified as sarcopenic.

Female patients ($n = 22$) were also shorter (163.5 ± 8.7 cm *vs.* 166.7 ± 5.9 cm, $p = 0.05$) but had a higher BMI (25.7 ± 4.2 *vs.* 23.0 ± 2.5, $p = 0.02$) than controls. Patients also had a lower ALM-index (6.30 ± 0.75 *vs.* 6.67 ± 0.55, $p = 0.05$), but their relative body fat mass (40.8 ± 7.6% *vs.* 32.0 ± 7.0%, $p < 0.001$) were higher. Fifty-nine percent of the women ($n = 13$) were classified as sarcopenic.

Conclusions: The body composition was altered toward lower skeletal muscle mass in patients with complex CHD. Approximately half of the patients were classified as sarcopenic. Contrary to men, the women had increased body fat and a higher BMI. Further research is required to assess the cause, possible adverse long-term effects and whether sarcopenia is preventable or treatable.

1. Introduction

Adults with congenital heart disease (CHD) is a growing and ageing population [1]. It is well known that the majority have a reduced aerobic exercise capacity [2]. The aerobic capacity depends on central as well as peripheral factors. Cardiac output is a central factor that is mainly dependent on ventricular performance and heart rate and it is most often reduced in patients with complex CHD. Further, peripheral muscle function, *e.g.* muscle endurance capacity and isometric muscle strength, have also been reported to be impaired [3–6].

Our research group as well as others showed previously that especially men with complex CHD were shorter, weighed less and had a higher prevalence of underweight than their peers. In a corresponding analysis in women, only those with tetralogy of Fallot were found to be shorter, whereas their weight and BMI did not differ from the general population [7,8].

Impaired skeletal muscle function together with the reported deviant anthropometric measurements can raise the question of an

Abbreviations: ALM, Appendicular Lean Mass; ALM-index, Appendicular Lean Mass-index; CHD, Congenital Heart Disease; DXA, Dual-Energy x-ray Absorptiometry; IPAQ, International Physical Activity Questionnaire; MET, Metabolic Equivalents.

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[1] All authors takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

https://doi.org/10.1016/j.ijcard.2019.06.011
0167-5273/

altered body composition regarding muscle and fat mass in adults with CHD. To assess body composition, Dual Energy x-ray Absorptiometry (DXA) is the most widely used technique in both clinical and research settings and it combines reproducible results with low cost and low exposure of ionizing radiation [9,10].

In the present study, we used DXA to investigate the body composition, and especially the skeletal muscle mass, in adults with complex CHD. Our hypothesis was that CHD patients with complex lesions have lower muscle mass that includes sarcopenia, and possibly higher fat mass than matched controls.

2. Material and methods

2.1. Study population

Seventy-three patients with complex CHD were recruited from centers specialized in congenital heart disease in Umeå, Uppsala and Lund in Sweden. Henceforth these are referred to as center I, II and III, respectively. The inclusion criteria were adults (≥18 years of age), clinically stable condition and complex CHD as defined by Erikssen *et al* [11]. Exclusion criteria were cognitive impairment affecting the independent decision capacity or the presence of genetic syndromes (*e.g.* Down Syndrome), comorbidity (*e.g.* rheumatoid arthritis) or other circumstances that affect study participation (*e.g.* pregnancy).

In center I, 91 patients with severe CHD were identified in the Swedish register of congenital heart disease (SWEDCON). Of these, 6 were excluded due to cognitive impairment or syndromes, 15 excluded due to comorbidity or other circumstances affecting participation, 15 declined participation, and 5 were not possible to reach. In total, 50 patients ($n = 15$ women) were included from center I. From center II, a convenience sample of 22 patients was identified, of whom 11 declined participation. In total, 11 patients were included from center II ($n = 5$ women). From center III, a convenience sample of 19 patients was identified, of whom 7 declined participation. In total, 12 patients were included from center III ($n = 2$ women). The total number of patients included in the study was 73 ($n = 22$ women) (Fig. 1).

An age and sex matched control was recruited for each patient. The controls were identified *via* the Swedish population register on the basis of residency in Umeå municipality, sex and same birthdate as each control. They were then contacted by phone and asked for participation if fulfilling the same criteria for inclusion and exclusion, except adult congenital heart disease, as the participants. Consequently, a total of 73 controls were included in the study ($n = 22$ women).

In a *post hoc* analysis no differences were found regarding age and sex distribution between participating patients and those who were excluded or declined. Corresponding analyses regarding controls rendered similar results (Data not shown).

All participants gave their written informed consent for study participation. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in *a priori* approval by the Regional Ethical Review Board, Umeå (Dnr 2016-18-31M, 2016-462-32M, 2017-203-32M).

2.2. Methods

2.2.1. Anthropometrical measures

Height and weight were measured in connection to assessment of body composition. Body Mass Index, the index "weight-for-height" (kg/m^2), was calculated and BMI ≥ 25 kg/m^2 was considered overweight as defined by the World Health Organization (WHO) [12]. Further, the waist-hip ratio was assessed according to the WHO data gathering protocol and ≥0.85 for women and ≥0.90 for men was defined as abdominal obesity as exemplified by WHO [13,14].

2.2.2. Body composition

Full and regional body composition was assessed with dual energy x-ray absorptiometry (DXA, Lunar iDXA, ME-200149, 210492, 210494, 212003, General Electrics Healthcare Madison, WI, US). Lean body mass was calculated as the total body weight minus bone and fat, thus representing the skeletal muscle mass. Appendicular lean mass (ALM) makes up the sum of lean mass in the arms and legs. To account for height, in the same way that obesity has been defined by dividing weight by height squared, relative lean mass was calculated by dividing ALM by height squared (ALM-index). To get the relative tissue fat, total fat mass was scaled to the sum of lean and fat mass. The abdominal fat was described in terms of visceral adipose tissue [15].

Sarcopenia, *i.e.* the loss of skeletal muscle mass by age or due to secondary causes, was defined according to Newman et al. [16]. In brief, we modeled the relationship between *ALM* and *height* (in meters) and *fat mass* (in kg) in a linear regression model in our reference group with men and women separately. The individuals identified by the 10th percentile of the residuals of the regression were defined as sarcopenic [16]. The linear regression models for ALM were $-28.82 + 29.95 \times height + 0.11 \times fat\ mass$ in men and $-17.12 + 20.69 \times height + 0.06 \times fat\ mass$ in women. By applying these models on our patients, and calculating the difference between their true and modeled ALM and using the previously described 10th percentile residual as cutoff, the sarcopenic patients were identified [9,16].

2.2.3. Isometric muscle force

The peak isometric muscle force was assessed on the dominant side for *m. biceps brachii* and *m. quadriceps* using a load cell (Ktoyo 333A-500, Ktoyo Co., Ltd., Gyeonggido, South Korea). For the biceps test, an inelastic strap was connected between the load cell and a handle that the test person held in his/her dominant hand. The test person stood with 90 degrees flexion in the elbow and the forearm while grasping the handle. They were instructed on command to perform a maximum elbow flexion and to hold the contraction for 5 s. For the quadriceps test, an inelastic strap was connected between the load cell and a strap attached around the ankle. The test person sat on a bench with back support and with 90 degrees of knee flexion. They were instructed on command to perform a maximum knee extension and to hold the contraction for 5 s. The unilateral grip strength was measured using a hand-held dynamometer (SAEHAN Digital Hand Dynamometer SH5003, Saehan Corp, Masan City, Korea). For each of the isometric muscle force tests, three repeated measurements were performed that were separated by 1 min of rest. The peak force was registered.

2.2.4. Self-reported physical activity

Self-reported physical activity was assessed using the short version of the International Physical Activity Questionnaire (IPAQ). The IPAQ comprises four generic items that regard time spent at different intensity levels of physical activity and a summary (vigorous, moderate, walking and total activity) in daily living during the past seven days. This was summarized as a continuous score of metabolic equivalents (MET) minutes/week [17]. Further, the patients were asked if they participated in regular exercise training. If so, information on type, frequency and duration was retrieved.

2.3. Statistics

All calculations were performed using the statistical package for the social sciences version 23–25 (SPSS, IBM corp., Armonk, NY, USA). Data were tested for normality and were presented as means, medians and ratios with standard deviations, range and interquartile range. Differences between groups were tested with Students *t*-tests for means, Mann-Whitney *U* test for ranks, and Chi-Square for ratios. The null hypothesis was rejected on *p*-values <0.05.

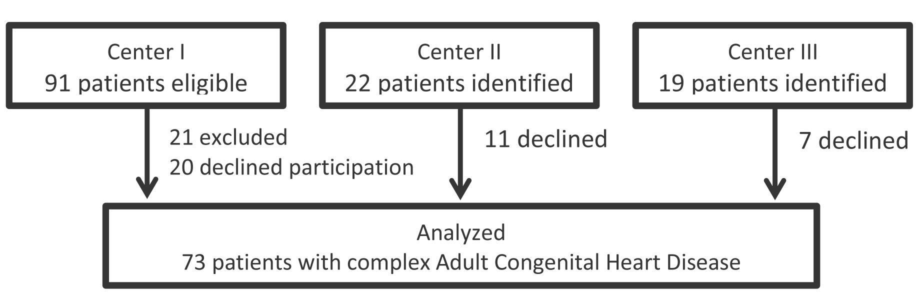

Fig. 1. Overview of inclusion process. In center I 91 patients with complex CHD were identified; 21 were excluded according to the exclusion criteria, and 20 declined participation or were not possible to reach. In center II, a convenience sample of 22 patients was identified; 11 declined participation. In center III, a convenience sample of 19 patients was identified; 7 declined participation. Thus, a total of 73 patients were included in the study.

3. Results

3.1. Baseline characteristics

Seventy-three patients with complex CHD, mean age 35.8 ± 14.3 years ($n = 22$ women, 30.1%), were included. The majority of the patients had previous surgical intervention related to their congenital heart disease and most were in NYHA class I-II ($n = 67$, 91.8%). Adults with congenital heart disease reported participation in regular exercise training at a lower extent and duration than controls; however, there were no difference in self-reported habitual physical activity according to IPAQ. In addition, no differences were found regarding smoking and snuff use. Reported usage of cardiovascular medication was more common in patients than in controls, and specifically the difference was found regarding ACE-inhibitors, beta blockers, diuretics, warfarin and aspirin (Table 1).

3.2. Anthropometric data

Adults with complex CHD was shorter compared to controls. Male patients weighed less, but in relation to height, their BMI was within normal range and their waist-hip-ratio was high but did not differ in comparison of controls. However, female patients had equal weight as their controls but had a higher BMI that defined them as overweight on group level. Further, their waist/hip-ratio was higher than controls which placed them as borderline abdominal obese (Table 2).

3.3. Body composition

In men, no differences between patients and controls were found in variables regarding body fat, *i.e.* total fat mass, tissue fat percentage and visceral adipose tissue. However, the variables describing their skeletal muscle mass, *i.e.* total lean mass, ALM and ALM-index, were all lower for male patients. In contrast, female patients had a higher total fat mass, tissue fat percentage and visceral adipose tissue compared to controls. Total lean Mass and ALM were lower for female patients, and correcting for their shorter stature, this also applied for their ALM-index (Table 2). Forty-seven percent of the male patients ($n = 24$) and 59% of the female patients ($n = 13$) were sarcopenic compared to 10% ($n = 5$) and 9% ($n = 2$) in their respective control groups ($p < 0.001$ for both).

In a sensitivity analysis the patients with an Arterial Switch for TGA ($n = 6$), with expected near normal exercise capacity [2], and those with extracardiac limitations ($n = 3$) were excluded. This analysis resulted in mainly unchanged results regarding the anthropometric data, DXA measurements and isometric strength presented in Table 2. The only notable change was that the slightly lower BMI for male patients turned out to be significantly lower than controls (23.6 ± 2.5 *vs.* 25.2 ± 3.9, $p = 0.032$).

3.4. Muscle strength

Patients with CHD had lower isometric strength in elbow flexion (*m. biceps brachii*), knee extension (*m. quadriceps femoris*) and hand grip compared to the control group. These differences also pertained for men and women separately (Table 2).

Table 1
Descriptives.

			Patients ($n = 73$)	Controls ($n = 73$)	*p*
Sex	Male	n (%)	51 (69.9)	51 (69.9)	1.000
Age		mean ± SD	35.8 ± 14.3	35.9 ± 14.3	0.973
Diagnosis	Fontan	n (%)	21 (28.8)		
	Tetralogy of Fallot	n (%)	20 (27.4)		
	d-TGA with atrial switch	n (%)	15 (20.5)		
	d-TGA with arterial switch	n (%)	6 (8.2)		
	cc-TGA	n (%)	4 (5.5)		
	Pulmonary atresia	n (%)	3 (4.1)		
	Eisenmenger	n (%)	1 (1.4)		
	Truncus arteriosus	n (%)	1 (1.4)		
	Miscellaneous	n (%)	1 (1.4)		
	AVSD	n (%)	1 (1.4)		
EF	>40%	n (%)	61 (83.6)		
	≤40%	n (%)	12 (16.4)		
Previous cardiac intervention		n (%)	69 (94.5)		
Age at intervention		mean ± SD	4.8 ± 5.4		
Other cardiac intervention[a]		n (%)	39 (53.4)		
NYHA	NYHA I	n (%)	48 (65.8)		
	NYHA II	n (%)	19 (26.0)		
	NYHA III	n (%)	3 (4.1)		
	Extra-cardiac limitation[†]	n (%)	3 (4.1)		
Regular exercise training		n (%)	31 (42.5)	46 (63.0)	**0.013**
Frequency Times/week		median (min-max)	0.0 (0.0–7.0)	2.0 (0.0–7.0)	**0.040**
Duration min		median (min-max)	0.0 (0.0 −150)	45 (0.0–120)	**0.029**
IPAQ MET/min/week		median (IQR)	1786 (2808)	1711 (2680)	0.681
Active smoker		n (%)	2 (2.7)	2 (2.7)	0.902
Active snuff user		n (%)	15 (20.5)	14 (19.2)	0.573
Cardiovascular medication		n (%)	44 (60.3)	6 (8.2)	**<0.001**
	ARB	n (%)	6 (8.2)	4 (5.5)	0.512
	ACE-i	n (%)	22 (30.1)	2 (2.7)	**<0.001**
	Beta blockers	n (%)	23 (31.5)	0 (0.0)	**<0.001**
	Diuretics	n (%)	13 (17.8)	1 (1.4)	**0.001**
	Warfarin	n (%)	17 (23.3)	0 (0.0)	**<0.001**
	Calcium channel blockers	n (%)	4 (5.5)	2 (2.7)	0.404
	Aspirin	n (%)	12 (16.4)	0 (0.0)	**<0.001**
	NOAC	n (%)	3 (4.1)	0 (0.0)	0.080
	Statins	n (%)	4 (5.5)	1 (1.4)	0.172
	PAH drugs	n (%)	2 (2.7)	0 (0.0)	0.154
	Nitroglycerine	n (%)	2 (2.7)	0 (0.0)	0.154
	Digoxin	n (%)	2 (2.7)	0 (0.0)	0.154
	Aldosterone inhibitors	n (%)	1 (1.4)	0 (0.0)	0.316
	Amiodarone	n (%)	1 (1.4)	0 (0.0)	0.316

Data are presented as *n* (%), mean ± SD, median (min-max) and median (IQR). Differences between groups are tested with Chi-Square test for ratios, Students *t*-tests for means and Mann-Whitney *U* test for medians. Bold p-values denotes $p < 0.05$. d-TGA indicates dextro Transposition of the Treat Arteries; cc-TGA, congenitally corrected Transposition of the Great Arteries; AVSD, Complete AV-septal defect; EF, Ejection Fraction of the systemic chamber; NYHA, New York Heart Association; IPAQ, The International Physical Activity Questionnaire; MET, Metabolic Equivalent of Task; ARB, Angiotensin Renin Blockers; ACE-I, Angiotensin Conversion Enzyme inhibitor; NOAC, New oral Anticoagulants; PAH, Pulmonary Arterial Hypertension. SD, Standard Deviation; IQR, Interquartile range; n, number.

[a] Angiography, Percutaneous Coronary Intervention, Cardiac Catheter intervention, Pacemaker or Implantable Cardioverter-Defibrillator.

[†] Limited by joint related problem while walking/running ($n = 2$), impaired balance related to previous stroke ($n = 1$).

4. Discussion

To the best of our knowledge, the present study is the first to show that adult patients with complex CHD not only have impaired muscle strength but also reduced muscle mass with a high prevalence of sarcopenia in spite of their young age. This finding is consistent with the reduced aerobic exercise capacity commonly found in this population [2,4]. In addition to a lower muscle mass, female patients showed a higher BMI and fat mass than controls. These findings may have potential prognostic and therapeutic implications. Furthermore, our data show that the chronic impact of congenital heart disease has effects beyond the cardiovascular system.

Table 2
Anthropometric data, DXA measurements and Isometric Strength.

	Total			Male patiens			Female patiens		
	Patient $n = 73$	Control $n = 73$	*p*	Patient $n = 51$	Control $n = 51$	*p*	Patient $n = 22$	Control $n = 22$	*p*
Height *cm*	173.2 ± 9.7	176.6 ± 9.2	**0.029**	177.4 ± 6.6	180.9 ± 6.7	**0.009**	163.5 ± 8.7	166.7 ± 5.9	**0.045**[a]
Weight *kg*	73.7 ± 11.8	76.6 ± 13.9	0.174	76.0 ± 10.8	82.0 ± 12.4	**0.011**	68.2 ± 12.5	64.1 ± 7.9	0.198
BMI kg/m^2	24.6 ± 3.4	24.5 ± 3.5	0.787	24.2 ± 3.0	25.1 ± 3.8	0.176	25.7 ± 4.2	23.0 ± 2.5	**0.017**
Waist *cm*	88.4 ± 10.3	86.2 ± 11.7	0.220	89.6 ± 10.1	90.1 ± 10.9	0.811	85.6 ± 10.6	77.0 ± 7.9	**0.004**
Hip *cm*	97.3 ± 8.5	96.6 ± 8.2	0.596	95.9 ± 6.2	97.4 ± 8.6	0.342	100.6 ± 11.8	94.9 ± 6.9	0.057
Waist/Hip-ratio	0.91 ± 0.07	0.89 ± 0.09	0.151	0.93 ± 0.07	0.93 ± 0.07	0.616	0.85 ± 0.06	0.81 ± 0.06	**0.030**
DXA fat measurements									
Total fat mass *kg*	22.9 ± 8.7	20.5 ± 8.7	0.101	20.9 ± 7.6	20.8 ± 9.6	0.916	27.5 ± 9.4	20.0 ± 6.4	**0.004**
Relative tissue fat mass *%*	31.8 ± 9.3	27.4 ± 8.7	**0.003**	27.9 ± 7.0	25.4 ± 8.6	0.107	40.8 ± 7.6	32.0 ± 7.0	**<0.001**
VAT-mass *g*	964 ± 649	789 ± 938	0.192	1033 ± 701	1011 ± 1037	0.902	805 ± 486	274 ± 248	**<0.001**
DXA lean measurements									
Total lean mass *kg*	48.3 ± 8.7	53.3 ± 9.6	**0.001**	52.6 ± 6.0	58.3 ± 6.3	**<0.001**	38.2 ± 4.4	41.6 ± 3.9	**0.011**
ALM *kg*	21.69 ± 4.70	24.95 ± 5.28	**<0.001**	23.84 ± 3.59	27.70 ± 3.57	**<0.001**	16.72 ± 2.82	18.57 ± 2.00	**0.017**
ALM-index kg/m^2	7.18 ± 1.08	7.92 ± 1.15	**<0.001**	7.57 ± 0.97	8.46 ± 0.90	**<0.001**	6.30 ± 0.75	6.67 ± 0.55	**0.049**[a]
Isometric Strength									
Biceps *N*	183 ± 62	213 ± 61	**0.004**	211 ± 52	243 ± 45	**0.001**	119 ± 24	142 ± 22	**0.002**
Quadriceps *N*	429 ± 142	507 ± 151	**0.002**	480 ± 134	559 ± 138	**0.004**	310 ± 70	387 ± 103	**0.006**
Unilateral grip *kg*	44 ± 13	51 ± 12	**0.002**	50 ± 10	57 ± 10	**0.001**	31 ± 7	38 ± 6	**0.001**

All numbers in mean ± SD. Students *t*-test used if not other specified. Bold p-values denote $p < 0.05$.
ALM, Appendicular Lean Mass; VAT, Visceral Adipose Tissue.
[a] Mann-Whitney U test.

4.1. Lean mass and sarcopenia

The lower lean mass conforms to the reduced muscle strength [3,6] and could possibly also explain the prior reports of a higher prevalence of underweight in men with CHD [5,7]. The most intuitive explanation to the lower lean mass and impaired muscle strength could simply be a past or present lower degree of muscle training. This is supported by the lower self-reported participation in structured exercise training among the patients in this study. However, previous research has shown that both children and adults with complex CHD, although they do report a lower degree of structured exercise training, still are as physically active as healthy controls, both self-reported and objectively measured [18,19]. Another possible explanation to a lower skeletal muscle mass could be a reduced response to the exercise training provided. Children and young adults with CHD do indeed improve fitness in terms of oxygen uptake and muscle strength in response to exercise training [20], but whether this is to the same extent as healthy peers has not been established. For acquired systolic heart failure, it has been shown that the skeletal muscle has a reduced oxidative capacity and impaired oxidative adaptations to endurance exercise, which suggest an overall impaired adaption to muscle training [21]. In opposition to acquired heart disease [22], CHD has a lifelong impact on the growing individual and possibly adverse effects on development of skeletal muscles; but whether results from cohorts with systolic heart failure are applicable to CHD is yet to be determined. However, we did not find a higher presence of sarcopenia in patients with moderately to severely reduced systemic ventricular function, EF ≤ 40% ($n = 12$), compared to those with normal or slightly reduced systemic ventricular function, EF > 40% ($n = 61$), (sarcopenia: 33.3%*vs.* 54.1%, $p = 0.188$). In summary, there are a number of plausible factors that may contribute to the lower skeletal muscle mass in this population. However, the impact of each factor remains to be established.

In acquired heart failure, low BMI is strongly associated with a worse prognosis [23]. Brida et al. also reported that a higher BMI and lower peak oxygen uptake were associated with lower all-cause mortality in patients with complex CHD [24]. We suggest that a link may be a higher skeletal muscle mass that serves as a physiologic reserve to handle the stress of chronic and acute illness. Also, in patients with Fontan circulation a lower lean mass and muscle strength may be particularly harmful as they depend on the skeletal muscle pump for venous return. Further research is needed to investigate the development of body composition over time and its association with prognosis. In addition, to determine the effect of interventions targeting skeletal muscle mass and strength, both in forms of muscle training and dietary supplementation, is of outmost importance, especially in the patients with Fontan circulation.

4.2. Fat mass and sex differences

We found that women with complex CHD have a slight tendency toward overweight. Similar results have been seen among female patients in populations of mixed but not in complex lesions [7,8,25]. More importantly we showed that women have a higher proportion of fat mass with a higher waist/hip-ratio and an increase in visceral adipose tissue, which suggest an unhealthy distribution around the waist. This is a troublesome finding since abdominal overweight is traditionally known to be a strong risk factor for acquired cardiovascular disease. The previously mentioned association between overweight and better prognosis is probably explained by cardiac cachexia and weight loss being linked to a high mortality, thereby leaving overweight as a marker but not a true cause of health [24]. It is also worth noting that the apparent positive effects of a high BMI has not been shown for men and women separately, so whether this is true for both sexes remains to be established; we strongly suggest further research to target the sex differences. Also, complications due to overweight will most likely be related to atherosclerosis and should be analyzed separately.

Healthy men and women do differ in body composition with females having higher proportions of body fat and this difference is observed in early childhood, accelerates in puberty and persists throughout life [26]. Children with complex CHD have lower weight and height just weeks after birth [27]. However, their overall growth pattern in terms of weight and height is highly variable and depends on sex and lesion. For example, female patients with tetralogy of Fallot have a catch-up in height in childhood, whereas girls with hypoplastic left heart syndrome and single ventricle physiology have a catch-up phase in weight and height in adolescence, with the former showing a decrease and the latter an increase in BMI [28]. We suggest that more uniform patterns with an abnormal development of skeletal muscle and fat mass over time would be found when examining the full body composition in these patients, and that the observed anthropometric deviations are only the tip of the iceberg.

The reason for the accentuated differences in body composition between men and female patients in our population suggests a contribution of hormonal factors. A previous report of a negative correlation between the growth hormone IGF-1 and cardiac output found in children and young adults palliated with Fontan procedure may lend support to this reasoning [29]. Additionally, numerous neuroendocrine hormones have been reported to be elevated in an adult population of CHD [30].

Another plausible explanation could be due to sex differences in physical activity. It is a common belief that women usually have a greater prevalence of physical inactivity than men, but in a recent study based on the WHO global health observatory data repository this could not be shown for the Swedish population [31]. Moons et al. found that in a cohort of a mixed variety of congenital heart lesions, men reported a higher participation in sports than women [8], and we saw the same tendency in our material albeit not statistically significant (*i.e.* regular participation in exercise training men 45.1% *vs.* women 36.4%, $p = 0.488$).

4.3. Limitations

The skew distribution in terms of sexes in our material (30% women), can partly be explained by a higher prevalence of men in the diagnoses studied. The SWEDCON database covers almost all congenital heart defects, especially the complex, and in the first sample considered for inclusion 35% were women. Women were not excluded and did not decline participation to a greater extent than men.

It could be argued that we should have used the definition of sarcopenia as proposed by Baumgartner as ALM-index, *i.e.* $\leq$7.26 kg/ht^2 for men and $\leq$5.45 kg/ht^2 for women [32]. Applying these criteria the proportion of the male patients reaching the definition of sarcopenia would still be 47.1% ($n = 24$) compared to a decreasing proportion of 5.9% ($n = 3$) in the control group ($p < 0.001$). However, for the female patients only 13.6% (n = 3) would classify as sarcopenic compared to none in the respective control group ($p = 0.073$). However, since experts argue that proportion body fat should be considered for women and those that are obese, and the female patients were predominantly overweight, we concluded that Newmans method would be the most appropriate [9]. Nevertheless, there are substantial differences in the alterations in body composition between men and women with complex CHD possibly owing to different etiologies and prognostic implications.

The cross-sectional design limits the clinical implications of our study. To eventually address the causes of sarcopenia, increased knowledge about muscle mass in infants, childhood and adolescence and the development over time is needed. The extent of further decay of skeletal muscle with ageing is also yet to be studied, as well as the consequences on morbidity and mortality. We encourage prospective longitudinal studies and hope to follow up our cohort in the future.

The use of DXA is the golden standard in studies of body composition. It provides a reliable measurement of body composition at the cost of a very low radiation dosage. The precision errors are as low as 1.5% for Lean and Fat mass. To avoid the risk of potential inter-equipment reproducibility, we used DXA-machines from the same manufacturer for all measurements. We also manually adjusted the software derived Regions of Interests for different body parts, as recommended, to avoid measurement errors in regional anlayzes [33].

5. Conclusion

We have shown that adults with complex CHD have a lower skeletal muscle mass, a higher prevalence of sarcopenia and impaired muscle strength compared to controls. We suggest that this is a result of the long-term chronical impact of complex CHD, although the underlying mechanisms remain unknown. We also found sex differences with an increased fat mass and BMI in women, whose significance as well as cause we can only speculate on. Both low muscle mass and increased fat mass may be possible to modify by interventions such as muscle training and dietary regimens. Perhaps the next step toward a longer and healthier life for adults with congenital heart disease lies in a more structured follow-up program promoting individualized training regimen and a healthy diet.

Declaration of Competing Interest

None.

Acknowledgements

We thank Roger Andersson and Mikael Therell of the Sports laboratory at Umeå University for assessment of tests. Robert Lundqvist and Niklas Johansson are acknowledged for their valuable assistance with statistics.

Sources of funding

This work was supported by the Swedish Heart-Lung Foundation (20100355, 20130472), the Heart Foundation of Northern Sweden, research foundation of The Swedish Heart and Lung Association (E140-15, E109-16, FA2017:13), research foundation of Healthcare Professions within Cardiology, Umeå University and Västerbottens läns landsting (the County of Västerbotten) (VLL-574081), and The research foundation VISARE NORR, (the Northern county councils Regional federation). Dr. Karna Johansson is supported by the County Council Region Norrbotten.

References

[1] A.J. Marelli, A.S. Mackie, R. Ionescu-Ittu, E. Rahme, L. Pilote, Congenital heart disease in the general population: changing prevalence and age distribution, Circulation. 115 (2) (2007) 163–172.

[2] A. Kempny, K. Dimopoulos, A. Uebing, et al., Reference values for exercise limitations among adults with congenital heart disease. Relation to activities of daily life–single centre experience and review of published data, Eur. Heart J. 33 (11) (2012) 1386–1396.

[3] M. Greutmann, T.L. Le, D. Tobler, et al., Generalised muscle weakness in young adults with congenital heart disease, Heart. 97 (14) (2011) 1164–1168.

[4] G.P. Diller, K. Dimopoulos, D. Okonko, et al., Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication, Circulation. 112 (6) (2005) 828–835.

[5] L.A. Kröönström, L. Johansson, A.K. Zetterström, M. Dellborg, P. Eriksson, Å. Cider, Muscle function in adults with congenital heart disease, Int. J. Cardiol. 170 (3) (2014) 358–363.

[6] C. Sandberg, U. Thilén, K. Wadell, B. Johansson, Adults with complex congenital heart disease have impaired skeletal muscle function and reduced confidence in performing exercise training, Eur. J. Prev. Cardiol. 22 (12) (2015) 1523–1530.

[7] C. Sandberg, D. Rinnström, M. Dellborg, et al., Height, weight and body mass index in adults with congenital heart disease, Int. J. Cardiol. 187 (2015) 219–226.

[8] P. Moons, K. Van Deyk, D. Dedroog, E. Troost, W. Budts, Prevalence of cardiovascular risk factors in adults with congenital heart disease, Eur J Cardiovasc Prev Rehabil. 13 (4) (2006) 612–616.

[9] A.J. Cruz-Jentoft, J.P. Baeyens, J.M. Bauer, et al., Sarcopenia: European consensus on definition and diagnosis: report of the european working group on sarcopenia in older people, Age Ageing 39 (4) (2010) 412–423.
[10] S. Guerri, D. Mercatelli, M.P. Aparisi Gomez, et al., Quantitative imaging techniques for the assessment of osteoporosis and sarcopenia, Quant Imaging Med Surg. 8 (1) (2018) 60–85.
[11] G. Erikssen, K. Liestol, E. Seem, et al., Achievements in congenital heart defect surgery: a prospective, 40-year study of 7038 patients, Circulation. 131 (4) (2015) 337–346 (discussion 346).
[12] Department of Nutrition for Health and Development, WHO. Global Database on Body Mass Index. An Interactive Surveillance Tool for Monitoring Nutrition Transition, 2006.
[13] World Health Organisation. Waist circumference and waist–hip ratio report of a WHO expert consultation, geneva, 8–11 december 2008. 2011.
[14] WHO. Definition, diagnosis and classification of diabetes mellitus and its complications: Report of a WHO consultation. Geneva, World Health Organization (WHO). 1999.
[15] T.G.C.Z. Lohman, Body composition measurement methods: dual-energy x-ray absorptiometry, in: S.B. Heymsfield, T.G. Lohman, Z. Wang (Eds.), Human Body Composition, 2 ed., Human Kinetics, Champaign, IL, 2005, pp. 63–78.
[16] A.B. Newman, V. Kupelian, M. Visser, et al., Sarcopenia: alternative definitions and associations with lower extremity function, J. Am. Geriatr. Soc. 51 (11) (2003) 1602–1609.
[17] International physical activity questionnaire. https://sites.google.com/site/theipaq. Updated Accessed May 2018.
[18] E.R. Hedlund, B. Lundell, L. Villard, G. Sjöberg, Reduced physical exercise and health-related quality of life after fontan palliation, Acta Paediatr. 105 (11) (2016) 1322–1328.
[19] L. Larsson, B. Johansson, K. Wadell, U. Thilén, C. Sandberg, Adults with congenital heart disease overestimate their physical activity level, Int J Cardiol Heart Vasc. 22 (2018) 13–17.
[20] N. Duppen, T. Takken, M.T. Hopman, et al., Systematic review of the effects of physical exercise training programmes in children and young adults with congenital heart disease, Int. J. Cardiol. 168 (3) (2013) 1779–1787.
[21] W.M. Southern, T.E. Ryan, K. Kepple, J.R. Murrow, K.R. Nilsson, K.K. McCully, Reduced skeletal muscle oxidative capacity and impaired training adaptations in heart failure, Physiol Rep. 3 (4) (2015) e12353, https://doi.org/10.14814/phy2.12353.
[22] A. Kato, Muscle wasting is associated with reduced exercise capacity and advanced disease in patients with chronic heart failure, Futur. Cardiol. 9 (6) (2013) 767–770.
[23] S. Kenchaiah, S.J. Pocock, D. Wang, et al., Body mass index and prognosis in patients with chronic heart failure: insights from the candesartan in heart failure: assessment of reduction in mortality and morbidity (CHARM) program, Circulation. 116 (6) (2007) 627–636.
[24] M. Brida, K. Dimopoulos, A. Kempny, et al., Body mass index in adult congenital heart disease, Heart. 103 (16) (2017) 1250–1257.
[25] J.B. Lerman, I.A. Parness, R.U. Shenoy, Body weights in adults with congenital heart disease and the obesity frequency, Am. J. Cardiol. 119 (4) (2017) 638–642.
[26] J.C. Wells, J.E. Williams, S. Chomtho, et al., Body-composition reference data for simple and reference techniques and a 4-component model: a new UK reference child, Am. J. Clin. Nutr. 96 (6) (2012) 1316–1326.
[27] C. Daymont, A. Neal, A. Prosnitz, M.S. Cohen, Growth in children with congenital heart disease, Pediatrics. 131 (1) (2013) e236–e242.
[28] D.C. Aguilar, G.W. Raff, D.J. Tancredi, I.J. Griffin, Childhood growth patterns following congenital heart disease, Cardiol. Young 25 (6) (2015) 1044–1053.
[29] C.M. Avitabile, M.B. Leonard, J.L. Brodsky, et al., Usefulness of insulin like growth factor 1 as a marker of heart failure in children and young adults after the fontan palliation procedure, Am. J. Cardiol. 115 (6) (2015) 8\16–820.
[30] A.P. Bolger, R. Sharma, W. Li, et al., Neurohormonal activation and the chronic heart failure syndrome in adults with congenital heart disease, Circulation. 106 (1) (2002) 92–99.
[31] P.C. Hallal, L.B. Andersen, F.C. Bull, et al., Global physical activity levels: surveillance progress, pitfalls, and prospects, Lancet. 380 (9838) (2012) 247–257.
[32] R.N. Baumgartner, K.M. Koehler, D. Gallagher, et al., Epidemiology of sarcopenia among the elderly in New Mexico, Am. J. Epidemiol. 147 (8) (1998) 755–763.
[33] M. Lohman, K. Tallroth, J.A. Kettunen, M.T. Marttinen, Reproducibility of dual-energy x-ray absorptiometry total and regional body composition measurements using different scanning positions and definitions of regions, Metabolism. 58 (11) (2009) 1663–1668.