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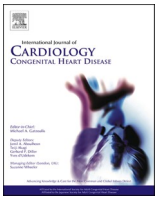

Increased carotid intima-media thickness and reduced health-related physical fitness in children and adolescents with coarctation of the aorta

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ABSTRACT

Background: Coarctation of the Aorta (CoA) was assumed to be one of the congenital heart defects not associated with major long-term sequels. Meanwhile, it is known that there are long-term cardiovascular consequences. This study investigates the functional outcome measures in children with CoA.

Methods: 77 children (40.3% girls, 13.1 ± 3.3 years) with CoA were examined for their functional outcome measures and compared to healthy controls (CG). Carotid Intima-Media wall thickness (cIMT) was measured by ultrasound of the common carotid artery. In addition, Health-related Physical Fitness (HrPF) was assessed by five tasks of the FITNESSGRAM® and health-related quality of life (HrQoL) was analyzed with a self-report questionnaire (KINDL-R).

Results: After adjustment for age and sex and in comparison to the CG, the CoA patients showed structural changes in cIMT (CoA: 0.480 ± 0.043 mm vs CG: 0.465 ± 0.033 mm; $p = 0.002$) and significantly lower HrPF (z-score −0.46 ± 0.7; $p < 0.001$; 32nd percentile). HrQoL in children with CoA was significantly better in comparison to CG ($p = 0.020$).

Conclusion: Early onset of structural changes of the cIMT in children with CoA could be shown. These structural changes in combination with hypertension, which often is associated with CoA, should be the focus of structured follow-up during childhood. The children with CoA showed impaired HrPF in comparison, where the promotion of physical activity should be the key factor for improvement. Encouragingly they showed better HrQoL.

1. Introduction

Coarctation of the aorta (CoA) occurs in around 4 out of 10,000 live births in Germany [1] and approximately makes 3.6% of all congenital heart defects [2]. In the past, CoA was considered as a simple discrete narrowing of the aortic isthmus that could be surgically corrected and was not associated with long-term complications. Meanwhile, CoA is recognized as part of an extensive aortic coarctation complex that almost always includes other anomalies throughout the left heart, the aortic valve, the aortic arch, and the vessel walls of various large arteries that supply the chest and head [3,4]. Even after successful correction CoA patients are at higher risk for long-term vascular impairments, higher cardiac morbidity [5] and show decreased long-term survival compared to healthy individuals [6]. CoA patients are exposed to the risk of ischemic stroke at a relatively young age and late neurological complications like subarachnoid bleeding [7]. CoA is often associated with vascular dysplasia, an abnormality of the vessel wall of the aorta and its larger branches. In the long term, this pathological wall structure leads to increased stiffness of the vessels and subsequently persisting systemic arterial hypertension even after successful CoA repair with minimal or no residual gradient [4]. The remaining arterial hypertension in CoA patients is most closely associated with adverse long-term events such as stroke [7] and myocardial infarction [8]. Since hypertension and its sequelae are already well studied in this population this study aims to investigate structural cardiovascular changes of the vessels and health-related physical fitness (HrPF), as well as health-related quality of life (HrQoL) in children and adolescents with CoA in comparison with healthy controls.

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2. Methods

2.1. Study participants

In this cross-sectional study, a sample of 77 children and adolescents with CoA (31 (40.3%) female, 13.1 ± 3.3 years) were included. The included study cohorts are shown in Fig. 1. Patients were recruited during their routine outpatient visits. The control group consists of 983 healthy children (498 [50.7%] girls, 11.8 ± 2.3 years) from the project "Sternstunden" and 1195 healthy children (562 [47.0%]) girls, 13.6 ± 2.2 years) from a recent school project (Table 1). All except 2 CoA patients were corrected at the time of the study and the Bethesda classification by Warnes et al. was used to categorise the severity of CoA in moderate or complex [9].

The children and adolescents with CoA and their guardians gave written informed consent to participate in the study. The study was conducted following the Declaration of Helsinki and was approved by the local ethical board of the Technical University of Munich (project number: 314/14). It is part of the FOOTLOOSE (German Clinical Trials Register ID: DRKS00018853) project, an ongoing, non-systematic study on the cardiovascular, metabolic and physical health of children and adolescents with CHD. Parts of the data have been published in previous studies comparing patients with various heart defects [10]. This study describes a detailed analysis of patients with CoA.

2.2. Measures of structural arterial stiffness

The wall thickness of carotid intima-media (cIMT) as a marker for structural changes of the vessel and early atherosclerosis, was assessed with B-mode ultrasound following the recommended guidelines [11]. Measurements were conducted with the semi-automated Cardiohealth Station from Panasonic (Yokohama, Japan), with patients lying in the supine position and the head turned 45° to the opposite of the examined side, the neck slightly tilted backwards. In the first step, the neck vessels were scanned for plaques cross-sectional. Afterwards, the common carotid artery was displayed in the longitudinal view. Pictures were taken of the cIMT on the far-wall, in the end-diastolic phase, ~1 cm proximal to the bifurcation in two angles on the right (120° and 150°) and left (210°and 240°) side of which an average was calculated.

2.3. Health-related physical fitness

HrPF was assessed by five tasks of the FITNESSGRAM® test battery in standardized order [12]. For all test items, FITNESSGRAM® is reported to have very good to generally acceptable criterion-referenced reliabilities and good validity [13]. It comprises 1. maximum repetition of curl-ups and 2. 90° push-ups for examining abdominal and upper limb strength. Truncal strength and flexibility were assessed by the 3. trunk-lift. The flexibility of the upper arm and shoulder girdle was assessed by the 4. shoulder stretch, the flexibility of the hamstrings was assessed by the 5. back-saver sit-and-reach test. The latter two tasks were performed separately with the right and left sides and mean scores were calculated afterwards. The subcategories flexibility (calculated out of the mean z-scores of back-saver sit and reach, shoulder stretch and trunk lift) and strength (calculated out of the mean z-scores of curl-up, push up and trunk lift) were calculated. Health and safety guidelines were followed and implementation was first shown and explained by the study conductor. Detailed information about the execution of the FITNESSGRAM® tasks can be seen in Supplement I.

Table 1
Anthropometric data of the CoA patients and the healthy controls.

Anthropometric data	CoA patients	Healthy controls	p-values
Number of Patients	77	2178	
Age (years)	13.1 ± 3.3	12.8 ± 2.4	0.310
Sex Female (%)	31 (40.3%)	1060 (48.7%)	0.147
BMI	19.14 ± 3.9	19.3 ± 3.5	0.742

CHD: congenital heart defect; CoA: coarctation of the aorta; BMI: body mass index.
p: level of significance with $p < 0.05$, significant values are bold.

2.4. Health-related quality of life

HrQoL was evaluated with the KINDL® questionnaire [14]. The KINDL® is a generic instrument that comprises 24 items referring to the last week. The KINDL® relates to the six domains physical well-being, emotional well-being, self-esteem, family, friends, everyday functioning. Questions are answered on a 5-point Likert Scale and a total score ranging from 0 to 100 was calculated whereby higher values reflect better HrQoL. Concerning the structure of the subscales, reliability and factorial validity for internal consistency, Cronbach's alpha reached $\alpha = 0.84$ overall, and for the subscales, it reached values around $\alpha = 0.70$. Convergent validity was tested in correlation with the Children Health Questionnaire [15], with the Life Satisfaction Questionnaire adapted for children [16] and the SF-36 [17] with a correlation of results ($r \geq 0.60$) concerning the subscales (with the Vitality and Emotional Well-Being subscales of the SF-36 and the FLZM with the General Well-Being subscale of the Child Health Questionnaire). The reported results were confirmed by other studies [18–20].

2.5. Data analysis

Descriptive data of the children with CoA and the healthy control group are presented in mean values, standard deviations (mean ± SD) and total numbers (%). A Student's t-test for independent samples was performed for descriptive comparison of anthropometric data between children with CHD and CG. Multivariable analysis of variance models with adjustment for sex and age were used for the comparison of CoA patients and controls in cIMT and HrQoL. The LMS method was applied for making the proficiency of girls and boys of various ages comparable in terms of HrPF [21]. It is based on the acceptance that observable distributions of measurements can be transferred through Box-Cox-Transformation into a standard normal distribution. To have the opportunity to include co-founders (age and sex) a generalization of the LMS method was used. The GAMLSS-model with acceptance of Box-Cox-Cole-Green-distribution is similar to LMS except it includes two factors [22]. Using this method the reference group for HrPF was calculated to the fiftieth percentile representing the reference standard for age and sex. The z-score transformation was done with all five tasks.

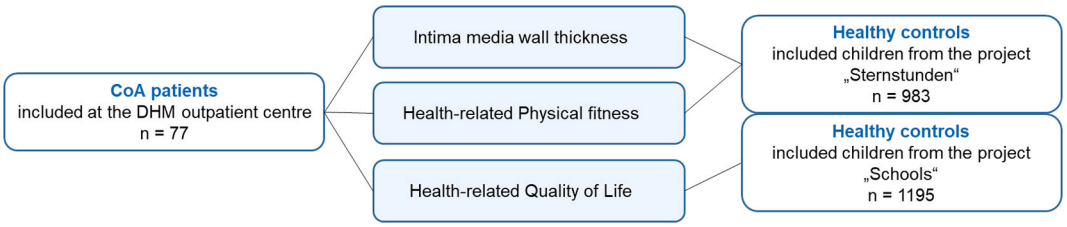


Fig. 1. Study population flow-chart. CoA: coarctation of the aorta; n: number.

The mean of z-scores of all five tasks represents the total HrPF z-score. Therefore, a Students t-test to "0" was performed to evaluate the significance of the difference between children with CHD and healthy control groups. Figures show results in pirate plots (represents mean, confidence interval, raw data and density distribution). All analyses were performed using the software SPSS V.28 (SPSS Inc., Chicago, Illinois, USA) or R software V. 3.3.1. and V. 4.1.1., additional with gamlss-package V. 5.0-2 of R software with the level of significance set to two-sided p-values <0.05 for all tests.

3. Results

The anthropometric data of patients with CoA and the healthy controls showed no differences in age, sex and body-mass index (BMI), (Table 1). Insights of the patients with CoA such as medical treatments and diagnoses are given in Table 2.

3.1. Measures of structural arterial stiffness

There were still structural changes shown in children with CoA, the cIMT was significantly thickened compared to the healthy control group (Fig. 2). On the contrary, patients with CoA presented normal blood pressure values, but 16 showed hypertension which is medically treated (Table 3).

3.2. Health-related physical fitness

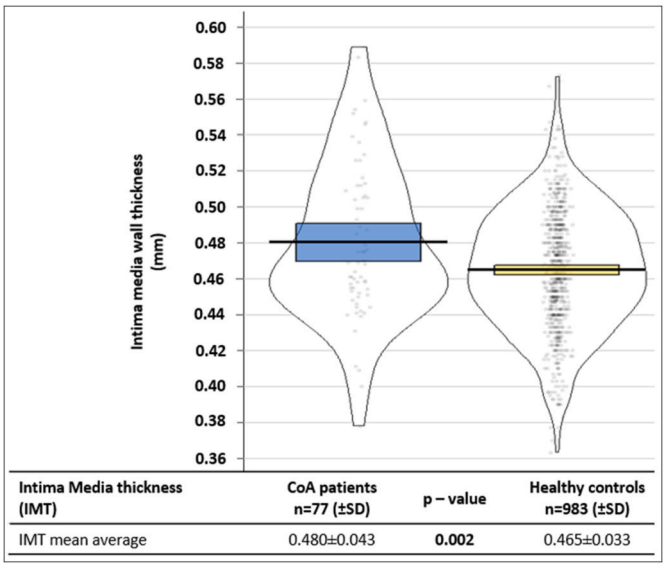
The total HrPF score was significantly reduced in children and adolescents with CoA compared to the healthy controls. The three flexibility tasks of FITNESSGRAM® were significantly reduced in means. Curl-ups showed no significant difference between CoA patients and the healthy controls and in 90° push-ups the CoA patients showed significantly better results. In the subgroups, flexibility and strength children with CoA were significantly impaired (Table 4).

3.3. Health-related quality of life

CoA patients showed significant higher HrQoL total scores than the healthy controls (CoA: 79.3 ± 7.9 vs CG: 75.7 ± 10.1; p = 0.020) as well as in the sub-domains physical well-being, emotional well-being and school (Fig. 3, below).

4. Discussion

The main findings of this study are that children with CoA showed functional impairment characterized as increased cIMT as well as decreased HrPF compared to healthy controls. HrQoL was high and even better than that of the control group, which is an encouraging finding.



Intima Media thickness (IMT)	CoA patients n=77 (±SD)	p – value	Healthy controls n=983 (±SD)
IMT mean average	0.480±0.043	**0.002**	0.465±0.033

Fig. 2. Comparison of the intima-media wall thickness of CoA patients and Healthy controls adjusted for sex and age
mm: millimetre; CoA: coarctation of the aorta; n: number; p: level of significance with p < 0.05, significant values are bold.

Table 3
Blood pressure and medication in patients with CoA and severity by Warnes [9].

Values	CoA total (±SD) n = 77	CoA moderate (±SD) n = 66	CoA complex (±SD) n = 11
Peripheral systolic blood pressure (mmHg)	113.8 ± 14.5	114.8 ± 14.5	107.0 ± 14.7
Peripheral diastolic blood pressure (mmHg)	64.47 ± 7.3	64.4 ± 7.7	65.2 ± 6.2
Hypertension	16 (20.7%)	13 (19.7%)	3 (27.3%)
Medication	9.1% beta-blocker 7.8% ACE-inhibitors	9.1% beta-blocker 9.1% ACE-inhibitors	9.1% beta-blocker

CoA: coarctation of the aorta; SD: standard deviation; n: number; mmHg: millimetre of mercury.

4.1. Structural arterial stiffness

Our findings of increased cIMT confirmed the previous results in a

Table 2
Exact description of the key clinical data of the patients with CoA.

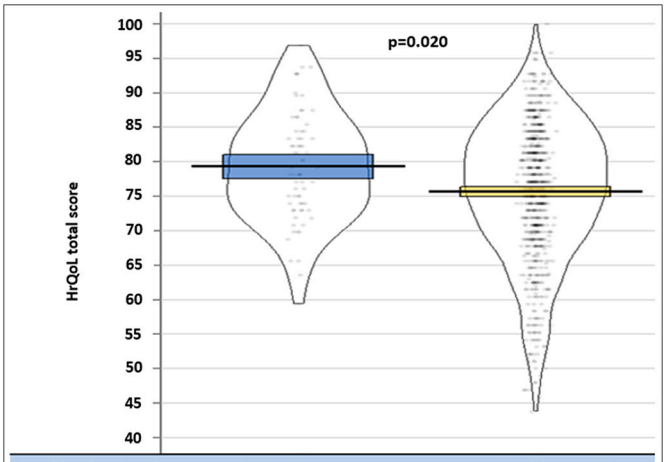
CoA Variables	CoA total	CoA	CoA bi	CoA vsd	CoA shone
Number of patients	77	28	30	10	9
Age at first surgery or catheter intervention (years)	1.22 ± 2.7	1.73 ± 3.4	1.1 ± 2.2	1.06 ± 3.2	0.08 ± 0.1
Type of repair (3 most frequent)	55.8%End-to-End-anastomosis 10.4% End-to-Side-anastomosis 9.1% Pericardial patch	50% End-to-End-anastomosis 11% End-to-Side-anastomosis 11% Pericardial patch	50% End-to-End-anastomosis 10% End-to-Side-anastomosis 13% Pericardial patch	70% End-to-End-anastomosis 10% End-to-Side-anastomosis 10% Subclavian flab	78% End-to-End-anastomosis 11% End-to-Side-anastomosis 11% Stent
Access-type of first intervention[a]	44 (57%) THL 21 (27%) ST 10 (13%) HK	71% THL 11% ST 14% HK	50% THL 30% ST 17% HK	70% ST 30% THL	67% THL 22% ST 11% HK
Number of surgeries (Min/Max)	1.29 ± 1.1 (0/6)	0.96 ± 0.5 (0/2)	1.13 ± 0.7 (0/3)	1.50 ± 1.0 (1/4)	2.67 ± 2.0 (0/6)
Number of catheter interventions (Min/Max)	0.63 ± 0.9 (0/3)	0.57 ± 0.9 (0/3)	0.62 ± 0.8 (0/3)	0.30 ± 0.7 (0/2)	1.22 ± 1.1 (0/3)

[a] 2 native patients; CoA: coarctation of the aorta; CoA bi: with additional bicuspid aortic valve; CoA vsd: with additional ventricle septal defect; CoA shone: with additional shone-complex; Min: minimum; Max: maximum; THL: lateral thoracotomy; ST: sternotomy; HK: heart catheter.

Table 4
Health-related physical fitness of children with CoA compared to CG.

Health-related physical fitness	z-score CoA patients	Percentile	p - values
Shoulder stretch (distance in cm)	−0.80 ± 1.3	21.	**<0.001**
Curl – up (number of repetitions)	−0.15 ± 1.2	44.	0.271
Trunk lift (distance in cm)	−0.69 ± 1.3	25.	**<0.001**
Back-saver sit and reach (distance in cm)	−0.82 ± 1.4	21.	**<0.001**
90° Push – up (number of repetitions)	0.28 ± 1.0	61.	**0.030***
Calculated z-score values	**z-score**	**Percentile**	**p-values**
Total HrPF z-score (z-means of all five tasks)	−0.46 ± 0.7	32.	**<0.001**
Strength (z-means curl-up, push-up, trunk lift)	−0.19 ± 0.7	42.	**0.038**
Flexibility (z-means shoulder stretch, back-saver sit and reach, trunk lift)	−0.78 ± 1.0	22.	**<0.001**

CoA: coarctation of the aorta; z-score: generalization of the LMS-method, the GAMLSS-model with acceptance of Box-Cox-Cole-Green-distribution including two factors (sex and age); p: level of significance with $p < 0.05$, significant values are bold. *significantly better in patients with CoA.



Health-related quality of life subscales	CoA patients (±SD)	p – values	Healthy controls (±SD)
physical well-beeing	82.2±13.8	**0.001**	75.3±15.4
emotional well-beeing	86.3±9.3	**0.043**	83.0±11.3
self-esteem	68.4±18.0	0.266	65.5±17.4
family	87.3±12.9	0.230	84.8±14.8
friends	78.7±14.4	0.920	77.8±14.4
school	73.9±16.2	**0.017**	67.7±17.3

Fig. 3. Multivariable analysis of variance model of Health-related Quality of Life in children with CoA compared with healthy controls adjusted for sex and age
CoA: coarctation of the aorta; SD: standard deviation; HrQoL: health-related quality of life; p: level of significance with $p < 0.05$, significant values are bold.

larger CoA patient cohort and are in concordance with other studies, where children with CoA showed increased cIMT values compared to healthy controls [10,23,24]. Sendzikaite et al. reported in a recently published study increased cIMT values in CoA children at a mean age of 12.3 years that correspond to healthy young adults at an age range of 20–30 years [24]. In our study cohort, structural changes of the vessel wall occurred even though peripheral blood pressure was normal. That can be attributed to the fact that the high pressure proximal to the isthmic stenosis is directly transferred to the outgoing common carotid arteries. This exposed the common carotid arteries to the high pressure during pregnancy, and remain until surgical or interventional correction. But also postoperatively, a certain restriction of the Windkessel function of the Aorta remains due to the correction, especially in the case of long-distance stenoses. Weymann et al. describe in this context the positive effects of implanting decellularised allografts to preserve the Windkessel function [25]. This Windkessel function restriction seems to have a more marked effect on the common carotid arteries earlier than is the case in the peripheral system, despite a slightly increased pressure gradient. Also, high pulse pressure can explain increased cIMT values, which is relevant in CoA patients even with normal peripheral blood pressure values [24].

It can be suggested that CoA patients should be corrected as early as possible to ensure relief of the common carotid arteries as early as possible. In addition, systematic control of cIMT should be performed, as increased cIMT values were shown to be predictive for myocardial infarction, cerebrovascular events, aortic aneurysm repair and cardiac death in adults with CoA [26]. These findings underline a prevalent risk for atherosclerotic heart disease in CoA children compared with the general population and demonstrate that structural changes in cIMT are present already in childhood.

4.2. Health-related physical fitness

This study showed reduced HrPF in CoA children, which is in concordance with the previous study in all kinds of CHD in children [27]. These results are not unexpected, as many studies report impaired physical activity, exercise capacity and developmental delay in children with CHD [28–32]. There was no association between HrPF and cIMT. Underlying causes of impaired physical fitness are multifactorial. Reduced HrPF may be a result of inpatient hospital stays, surgeries and rehabilitation disrupting the early critical period of development [33]. Through a lack of movement experience, children may be hindered from reaching developmental milestones. These display the foundation of motor ability, the base for building a capacity for more complex movement patterns [34] and also represent the main component of lifelong active lifestyle promotion [35,36]. The significant impairment of upper body flexibility may be attributed to undergoing open-heart surgery, including sternotomy and/or thoracotomy, which leads to postoperative consequences such as chest pain and sternal instability and promotes the adoption of a relieving posture. This posture indicates hyperkyphosis of the entire spine in particular the thoracic spine with prolongation to the shoulder girdle. Unfortunately, the high majority of patients with lateral thoracotomy does not allow for a subgroup analysis but should be suggested in the future, additionally, it would be interesting if reduced HrPF is associated with exercise capacity measured via CPET in future studies. Another aspect in terms of reduced HrPF is overprotection by parents and medical doctors even physical activity and exercise are recommended in children with CHD [37,38]. To reduce the risk of posture and motor problems in CoA patients, early and longitudinal monitoring of motoric development is indicated to provide adequate early support [39] and to avoid, limitations to track into adolescence and adulthood.

4.3. Health-related quality of life

HrQoL should be in the centre of patient care and has been studied extensively in pediatric patients with CHD in recent years. However, inconclusive findings between studies remain, mainly attributed to widespread methodological weaknesses in research on QoL in CHD patients [40]. Our study showed good HrQoL scores in CoA children, even superior to those in healthy controls, which is in line with other studies showing good self-reported HrQoL in children with CHD [41–43]. However, some studies report impaired QoL in CHD children compared to healthy controls [44,45], particularly in psychosocial, emotional, and

school functioning realms [41]. Differing results concerning HrQoL may be related not only to methodological limitations but also to the situation and environment in which patients were at the time of data collection. HrQoL scores differed if they filled in the questionnaires during their stay in the hospital or during routine follow-up at outpatient centres [46]. As this study has been conducted during routine follow-ups in the outpatient centre, this may favour the good HrQoL results in our study. Enhanced HrQoL in CoA children may be explained by improved coping strategies, as children and their families had to cope with the heart condition since the day of birth. In this context, an improved sense of coherence, as well as a high estimation of physical wellbeing associated with mindfulness, has also been reported [47].

5. Conclusion

Although children with CoA, showed better HrQoL compared to healthy children of the same age, early onset of structural changes of the cIMT was found. These structural changes in combination with hypertension, a common comorbidity of patients with CoA, should be the focus of structured follow-up monitoring to prevent cardiovascular morbidity at an early age. Also, the impaired HrPF should be addressed with physical activity promotion.

Limitations

The study results must be considered in the context that individual components of the CoA complex can vary widely in severity, resulting in a very distinct early and long-term course in CoA patients [3,4]. The study participants were recruited during regular follow-up care at the outpatient centre of the German Heart Center. CHD patients have been encouraged to be physically active in our tertiary centre for many years.

Contribution

Conception and design of the study: JM. Acquisition of data: JR, LW, JM. Analysis and interpretation of data: JR, JM. Drafting the article: JR, LW, JM. Revising it critically for important intellectual content: All Final approval of the version: All Supplement I: Detailed information about the execution of the FITNESSGRAM® tasks.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcchd.2022.100390.

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