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Investigation of flow-mediated vasodilatation (FMD) and comparison with carotid intima-media thickness (CIMT) in children with cyanotic congenital heart disease

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OriginalArticle

Abstract

BACKGROUND: There is a high mortality rate in cyanotic patients with congenital heart disease (CHD) due to cardiovascular complications. The cardiovascular prognosis is negatively affected by endothelium dysfunction, increased arterial stiffness, and impaired vascular system. This study aimed to determine carotid intimal mean thickness (CIMT) and flow-mediated dilatation (FMD) in a group of children with cyanotic CHD (CCHD).

METHODS: FMD and CIMT were evaluated for 45 children with CHKD and 38 patients who did not have CHKD over the period 2021 to 2022, as part of this case-control study. In terms of age and gender, the case group has been compared to controls.

RESULTS: Men accounted for 61.3% of the participants, with a mean standard deviation age of 7.8 5.39 years. In subjects with CCHD, CIMT increased non-significantly and FMD decreased significantly, but systolic blood pressure was significantly higher in patients than in the healthy group. (P=0.003).

CONCLUSION: FMD was reduced in children with CCHD, but in controls, systolic blood pressure and CIMT were lower. The risk of developing atherosclerosis in CCHD patients may be increased by an increase in CIMT and systolic blood pressure.

Keywords: Congenital Heart Defects; Flow-Mediated Dilatation; Cyanosis; Carotid Intimal-Media Thickness; Vascular Endothelium

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Introduction

Significantly, functional, gross primary irregularities of the heart or the substantial intrathoracic vessels present at birth lead to congenital heart disease (CHD)[1,2]. The prevalence of CHD worldwide is stated to be almost 0.8% to 1.2% of live births, and its incidence in developing countries located in Asia and Africa is comparatively higher than in most developed countries[3]. Based on the presence or absence of cyanosis, CHDs are divided into two main categories: Acyanotic CHDD and CCHD. Children with CCHD may present with cardiovascular collapse, congestive heart failure (CHF), cyanosis, cyanotic spells, or combinations of these presentations.

Some patients may have pure versions of certain defects, but most have different combinations. Most combinations have a high chance of poor outcomes[2,4].

Flow-mediated dilatation (FMD) of the brachial artery along with measurement of carotid intima-media thickness (CIMT) has been suggested as a surrogate marker for the diagnosis of early atherosclerosis[5].

These methods are non-invasive and evaluate endothelial function and structure, respectively[6].

Previous studies and researchers have shown the relationship between increased CIMT and cardio-vascular disease risk factors such as hypertension, metabolic syndrome, and dyslipidemia.

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Also, it has been reported that FMD correlates with impaired endothelium-dependent relaxation in the coronary arteries[7-9]. One of the first symptoms of atherosclerosis is endothelial dysfunction, which probably has a significant contribution to the development and clinical manifestation of atherosclerosis symptoms [10].

Studies have investigated children with CHD and the occurrence of cardiovascular diseases and their relationship with CIMT and FMD. Therefore, this research aims to investigate FMD in children with CCHD and its relationship with CIMT.

Methods

Participants

In 45 patients with CCHD, this case-control study was carried out. In two medical education clinics at Isfahan University of Medical Sciences, it was obtained by unrandom sampling. (the pediatric clinic of Imam Hossein and Shahid Chamran hospitals) and using the CHD registry in Isfahan[11] during 2021-2022. Additionally, thirty-eight healthy subjects were selected from the patient's relatives who were similar to the illness group in terms of age and gender. The inclusion criteria included children of both sexes, age at the start of the study under 18 years, and consent to participate. The exclusion criteria were pulmonary hypertension, systemic hypertension, and a history of taking diuretics, nitrates, sildenafil, or lipid-lowering drugs.

this investigation was approved by The ethics committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1400.102). This study met the standards of ethical conduct of the Declaration of Helsinki for patient welfare. The study was explained to the participating children to the extent of their understanding, and consent was collected. All parent's subjects in the study signed a written informed consent Before registration.

Checking of information on demographic and anthropometric

In this study, a checklist was prepared by a trained individual to record the name, contact information, age, sex, height, and weight of all patients and controls to calculate their body mass index (BMI).

Determination of Carotid Intima-Media Thickness (CIMT)

Using the Bmode system(MEDISON echo 7; Samsung, Korea) with a 10 MHz linear transducer, an ultrasound scan of the carotid artery was performed. All measurements were performed by the pediatric cardiologist. At this stage, the bilateral carotid artery was examined and CT was performed at the bifurcation level in the common carotid arteries. The image was concentrated on the peripheral wall of the artery, with CIMT defined as the distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line. In the diastolic phase, the thickness of the intima-media was checked on the longitudinal views of the peripheral wall of bilateral distal common carotid arteries (1-3 cm close to the carotid bifurcation). Considering that CIMT was measured three times, the combined mean of right and left common carotid arteries was analyzed.

Evaluation of Flow-Mediated Dilatation (FMD)

According to recent guidelines1, flow-mediated dilation was evaluated[11]. To visualize the best brachial artery, the arm was placed in an extended and motionless position, and scanning was performed from the brachial artery in the longitudinal part 3.5 cm above the anterior fossa.

The skin has been identified as a reference for subsequent measurements. The skin has been designated for reference to subsequent measurements after optimal positioning of the transducer. An average recording of three consecutive measurements was carried out over a continuous cardiac cycle. Any change in brachial artery diameter after 60 seconds of reactive hyperemia compared with the baseline measurement after deflation of a cuff around the forearm that was inflated to 50 mmHg above systolic blood pressure for 5 minutes was recorded as FMD. Before the inflation of the cuff, the response of the vessel diameter to reactive hyperemia was reported as a percentage change compared to its size. Following reactive hyperemia, the percentage change in the internal diameter of the brachial artery was initially reported as flow-induced dilatation.

The amount of change in the internal diameter of the brachial artery after reactive hyperemia was initially reported as flow-induced dilatation.

Statistical analysis

All tests were performed with SPSS statistics version

25.0. Quantitative variables are expressed as mean ± standard deviation and qualitative variables as numbers and percentages. After assessing the normality by the Shapiro Wilk test and QQ plot, the student's t-test and one-way analysis of variance (ANOVA) assessed differences between independent groups for normally distributed quantitative variables, Mann-Whitney's U-test and Kruskal Wallis test for variables with non-normal distribution, and the chi-square or Fisher exact test for qualitative variables. All results were considered statistically significant at the level of $P < 0.05$.

Results

A total of 75 subjects (61.3% male) were under the study (45 children with cyanotic heart disease and 30 control people). The mean age (SD) of the subjects under study was 7.8 (5.39) years, ranging from 1 to 20 years. There was no significant difference between the two studied groups in terms of gender and age (P=0.438). Also, the weight in the control group was higher than in the patient group, but this difference was not significant (P=0.052). However, the difference in height and body mass index was found to be significant (P<0.0001). Most of the patients (40%) were diagnosed with pulmonary atresia. The parameters of the enrolled subjects are summarized in Table 1.

Table 2 compares the CIMT of both groups. The mean CIMT for patients with cyanotic heart disease in the case group was higher than the control group, but it was not statistically significant (P=0.074).

When comparing diastolic and systolic blood pressure in the two groups, the results showed that in the patient group, systolic blood pressure was significantly higher than in the control group (P=0.003). However, there was no significant difference in diastolic blood pressure between the two groups (P=0.535) (Table 2).

The patients were classified into two groups: those with tetralogy of Fallot and those with pulmonary atresia after repair surgery. When comparing these three groups (pulmonary atresia, tetralogy of Fallot, and control), a significant difference in CIMT was found (P=0.035). In particular, the CIMT in patients with pulmonary atresia was very high compared to a control group. (P=0.008) (Table 3).

Also, the mean FMD in the two groups was not significantly different (P=0.335). Similarly, the comparison of FMD between the three groups (pulmonary atresia, tetralogy of Fallot, and control) was not significant y(P=0.606) (Table 3).

Table 1. characteristics of participants

Characteristics	Case (n=45)	Control (n=38)	P-value
Gender N (%)			
Male	31 (70.5)	20 (54.1)	0.167*
Female	13 (29.5)	17 (45.9)	
Age [Year]. Mean±SD	4.45 ± 2.54	5.88 ± 4.43	0.438^
Weight [Kg]. Mean±SD	17.28 ± 10.14	25.28 ± 17.02	0.052^
Height [Cm]. Mean±SD	86.75 ± 21.47	112.42 ± 28.35	<0.0001$
BMI[1] Mean±SD	22.45 ± 2.2	17.81 ± 3.6	<0.0001^
Diagnosis N (%)			
Tetralogy of Fallot.	27 (60)	-	-
Pulmonary atresia	18 (40)	-	-

[1]Body mass index *chi square test ^ Mann-Whitney's U-test $ Student's t-test

Table 2. Clinical characteristics of participants

Clinical characteristics	Case (n=45) Mean±SD	Control (n=38)	P-value
CIMT[1] (mm)	0.38±0.08	0.35±0.1	0.074^
FMD[2]	0.065±0.018	0.069±0.019	0.335$
Systolic blood pressure	105.95±12.86	98.81±9.33	0.003^
Diastolic blood presure	62.68±12.09	64.47±9.06	0.535^

^ Mann-Whitney's U-test $ Student's t-test

[1] Carotid intima-media thickness

Table 3. Comparison of CIMT and FMD between three groups

Characteristics	Group	Mean±SD	P-value
CIMT (mm)	Tetralogy of Fallot. (N=27)	0.37±0.9	0.035*
	Pulmonary atresia (N=18)	0.42±0.7	
	Control (N=38)	0.35±0.1	
	Tetralogy of Fallot. (N=27)	0.37±0.9	0.074^
	Pulmonary atresia (N=18)	0.42±0.7	
	Pulmonary atresia (N=18)	0.42±0.7	0.008^
	Control (N=38)	0.35±0.1	
	Tetralogy of Fallot (N=27)	0.37±0.9	0.367^
	Control (N=38)	0.35±0.1	
FMD	Tetralogy of Fallot. (N=27)	0.064±0.01	0.606&
	Pulmonary atresia (N=18)	0.066±0.01	
	Control (N=38)	0.069±0.02	
	Tetralogy of Fallot. (N=27)	0.064±0.01	0.958$
	Pulmonary atresia (N=18)	0.066±0.01	
	Pulmonary atresia (N=18)	0.066±0.01	0.902$
	Control (N=38)	0.069±0.02	
	Tetralogy of Fallot (N=27)	0.064±0.01	0.580$
	Control (N=38)	0.069±0.02	

^ Mann-Whitney's U-test $ Student's t-test & ANOVA $ Kruskal Wallis test

Discussion

The present study has shown that in children with CCHD, which is considered a gold standard for evaluating endothelial function, FMD, in conduit arteries, has decreased significantly[13]. Previous studies using different techniques have investigated endothelial function in CHD patients in different age groups[14-16].

The physiology of the brachial artery has been used to investigate endothelium function, including a pediatric cohort where FMD was shown to be significantly decreased in the cyanotic group and is supported by our studies on the reduction of FMD.

However, it was not in line with statistical analysis[15]. The average FMD was equal to the normal group in the two adult studies and showed no changes[17,18], and Other studies showed that FMD was significantly more common in the migraine, syncope, and syncope and migraine groups than control group[19].

Age and disease processes may be associated with differences in FMD measures observed between the current study and adult investigations, requiring further studies.

A preliminary study suggested a lower atherosclerotic burden in CHD patients compared to the general population. In these studies, the incidence of atherosclerosis in a sample of patients aged 11 to 44 years was evaluated based on CIMT measurements, coronary angiography, endothelial function, and lipid profiles as well as[15,20-23].

However, the present paper is the first to comprehensively investigate some signs of atherosclerosis in children under 18 years old with CHD. Based on the results of the coronary angiograms, some studies have shown that there is no evidence of coronary artery disease; however, in patients with CHD, the coronary arteries are twisted and narrowed, which makes it difficult to detect plaque on the coronary angiograms[20,22,23]. In addition, the burden of atherosclerosis can not be quantified by visually evaluating a coronary angiogram.

CIMT is a non-invasive assay to detect subclinical atherosclerosis. It may significantly help in diagnosing the status of patients with atypical chest pain or patients with several cardiovascular risk factors[24-26]. An increase in the mean of CIMT was observed in patients compared to the healthy group, which was not statistically significant. CIMT was assessed in Çiftel et al.'s investigation similar to our study, they showed CIMT was non-significantly increased in eighteen children with irreversible pulmonary hypertension due to congenital heart disease, while Meyer et al. demonstrated that CIMT in the right common carotid, left common carotid, right common carotid bifurcation, and common carotid bifurcation

in patients with a history of coarctation of the aorta and repair, who were between 6 and 17 years old, compared to the control group with 6 to 11 years of age were respectively: 0.48, 0.44, 0.52, and 0.48 compared to 0.38, 0.38, 0.39, and 0.39 mm in all 4 parts. This difference was highly significant[27]. Sabri et al. reported a considerable augmentation in CIMT in patients with premature coronary arterial disease[28]. Moreover, Reiner et al. found that even after controlling for confounding factors such as age, sex, height, and weight, children with a history of congenital heart disease still had higher CIMT than controls[29].

The results of the current experiment showed that when comparing CIMT among three groups of study subjects, including Tetralogy of Fallot, Pulmonary atresia, and control, the numerical average of CIMT in Tetralogy of Fallot and Pulmonary atresia was considerably higher than in the control group. This is consistent with observations from de Groot et al. and Nielsen et al., who found that children with repaired Tetralogy of Fallot and patients with Pulmonary arterial hypertension had a higher average CIMT, which causes changes in peripheral vascular[30-32]. However, another study by Tarp et al. suggested that people who underwent surgery in childhood due to congenital CHD are protected from atherosclerosis in adulthood, and their CIMT is low[22,33].

In the CCHD group, there were more increases in systolic blood pressure and BMI than in the healthy group. Similar to our research, Eikendal and Gianini et al. reported that disturbances in anthropometry, systolic blood pressure, and increased cholesterol in adolescents and pre-puberty children could be associated with increased CIMT[34,35]. Moreover, Kamel et al. demonstrated that there is a positive correlation between elevating CIMT and BMI in children with idiopathic nephrotic syndrome[36].

According to the studies mentioned above and the results obtained in the present study, there may be a correlation between the increase of CIMT and dysregulation of systolic blood pressure in children with CCHD. This relationship leads to the risk of atherosclerosis, which requires more experimentation.

Conclusions

To sum up, Brachial artery FMD and CIMT non-significantly declined and increased in CCHD children, respectively. Increased CIMT and systolic blood pressure may be a risk of developing atherosclerosis in CCHD patients. Further prospective studies with clinical outcomes are needed to assess the nature and significance of endothelial dysfunction in children with CCHD.

Abbreviations

CHD: congenital heart disease
CCHD: Cyanotic Congenital Heart Disease
CIMT: Carotid-intima-media-thickness
FMD: Flow-mediated dilatation
CHF: congestive heart failure

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Conflict of Interest

The authors declare no other competing interests.

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Author's Contributions

Conceptualization: N Navabfar, M Ghaderian. Methodology: A Ahmadi. Project administration: N Navabfar, M Ghaderian. Data curation and format analysis: N Navabfar, M R Sabri, Ch Mahdavi. Writing original draft: N Navabfar. Writing-review and editing: B Dehghan, M Ghaderian. Approval of final manuscript: All authors. Software: B Dehghan

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