Original Article

Comparison of CIMT and FMD in the Brachial Artery between Children with Acyanotic Congenital Heart Disease and Healthy Controls: A Case-Control Study

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Abstract

Background: *Congenital heart disease (CHD), a developmental abnormality of the heart and vessels, is encountered in the pediatric age group frequently. Brachial artery flow-mediated dilation (FMD) and carotid intima-media thickness (CIMT) are indicators of subclinical cardiovascular disease and are used as surrogate measures of subclinical atherosclerosis. The present study aimed to compare CIMT and FMD between children with acyanotic congenital heart disease (ACHD) and healthy controls.*

Methods: *A case-control study on 50 children with ACHD and 43 healthy individuals was done in Isfahan, Iran, between 2021 and 2022. The case group was selected via non-random sampling, and healthy controls were recruited from the relatives of the patients. A checklist, including age, sex, body mass index, and blood pressure, was filled out for all the participants. Then, FMD and CIMT were measured with brachial and carotid artery ultrasonography.*

Results: *Fifty children with ACHD and 43 healthy individuals (controls) under 18 years old participated in this study. Of these, 44 (47.3%) were girls and 49 (52.7%) were boys. The mean FMD was significantly higher in the ACHD group than in the control group (0.084±0.027 vs 0.076±0.042; P=0.021; 95% CI, 007 to 0.122;). CIMT was significantly higher in the ACHD group than in the control group (0.39±0.12 vs 0.34±0.1; P=0.037; 95% CI, 0.009 to 0.102;). However, systolic and diastolic blood pressure did not show differences between the groups.*

Conclusion: *Based on our results, CIMT and FMD assessment may help detect early changes in peripheral vessels associated with atherosclerosis in the future in ACHD. Further studies are needed to confirm our findings.*

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Keywords: *Heart defects; Congenital; Vasodilatation; Carotid intima-media thickness; Atherosclerosis*

Introduction

In the last decade, cardiovascular disease (CVD) has been a major cause of death and health costs in industrialized countries.[1, 2] The progression of atherosclerosis, a principal cause of CVD, commences in the early years of life and

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continues for a long time invisibly and without clinical symptoms. Accordingly, identifying individuals at risk is crucial to preventing the occurrence and development of this disease.[3-5] Several studies have shown that early atherosclerosis can be detected in children with congenital heart disease (CHD).[6] A developmental abnormality of the heart and great vessels, CHD is encountered in the pediatric age group frequently. The disease can be classified into cyanotic CHD and acyanotic CHD (ACHD). The incidence of CHD is estimated to be about 5 to 8 per 1000 live births.[7-10] ACHD with a left-to-right shunt has 3 types: ventricular septal defect, atrial septal defect, and patent ductus arteriosus. ACHD with obstructive lesions are considered coarctation of the aorta and valvular or supravalvular aortic stenosis.[11-13]

Endothelial dysfunction plays a role in every step during the atherosclerotic process, even in the early stages before the atherosclerotic plaque has developed.[14-16] Brachial artery flow-mediated dilation (FMD) is a well-studied measure of endothelial function and helps determine cardiovascular risk. Similarly, increased carotid artery intima-media thickness (CIMT), considered an early phase of atherosclerosis, is correlated with cardiovascular risk and coronary atherosclerosis severity.[15, 17-20] A few researchers have examined the relationship between FMD and CIMT in Iranian patients with ACHD. Accordingly, we aimed to compare the efficacy of CIMT and FMD in children with ACHD vs healthy controls.

Methods

The present case-control study was conducted at the pediatric clinic of Imam Hossein and Shahid Chamran hospitals, affiliated with Isfahan University of Medical Sciences, Isfahan, Iran, from 2021 through 2022 via available sampling. The study protocol was approved by the Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1399.622), and the study participants' welfare was ensured by adherence to the ethical conduct standards of the Declaration of Helsinki. Fifty patients with ACHD were selected through non-random sampling, and 43 healthy controls were recruited from the relatives of the patients. The nearest neighbor matching method was employed for age, sex, and body mass index. The inclusion criteria were all children under 18 years and consent to participate in the study. Individuals with hypertension, malignant pulmonary hypertension, and a history of taking diuretics, nitrates, and lipid-lowering drugs were excluded from the research.

In a pre-prepared checklist, the study population's anthropometric characteristics, including height, weight, and body mass index, and demographic indicators, such as age and sex, were recorded.

CIMT measurements were performed via B-mode ultrasonography (MEDISON EKO 7; Samsung, Korea) with a high-resolution, 10 MHz linear array transducer in all the patients. The measurements were taken while the subjects were in the supine position, with their necks rotated to the opposite side. A single trained pediatric cardiologist fellow, blind to the participants' clinical characteristics, took the measurements in a dark, quiet room. The region of interest for measuring the CIMT of the right and the left common carotid arteries was selected 1 cm proximal to the common carotid artery bifurcation. Three CIMT measurements were made on the near and far walls of the left and right common carotid arteries, carotid bifurcation, and internal carotid. The mean CIMT was calculated by averaging the values of the CIMT measured.

The FMD of the brachial artery was evaluated according to the guidelines of a prior study.[21] The resting diameter of the right brachial artery was measured 3 to 5 cm above the antecubital fossa. Next, a blood pressure cuff was inflated around the right forearm to at least 50 mmHg above the systemic blood pressure for 4 to 5 minutes. Forty-five to 60 seconds after cuff release, the diameter of the brachial artery was measured. The brachial FMD was calculated as the percentage of change in the maximum post-occlusion diameter of the brachial artery relative to the mean baseline diameter.

The SPSS (Statistical Package for the Social Sciences, version 25.0) software was used for all the statistical calculations. The results are reported as means, standard deviation (SD), frequencies, and percentages. The Kolmogorov-Smirnov test was utilized to determine the distribution characteristics of continuous variables. Differences between the groups were analyzed with the Student t test (for normal distribution), the Mann Whitney U test (for variables different from normal), and the χ^2 test or the exact Fisher test (for qualitative data). Additionally, the receiver operating characteristic (ROC) curve and its area under the ROC curve (AUC) were assessed for CIMT and FMD to determine their ability to discriminate between the 2 groups. Statistical significance was defined as a P value of less than 0.005.

Results

The study population consisted of 50 children with ACHD and 43 healthy individuals (controls). There were 44 (47.3%) girls and 49 (52.7%) boys. Atrial septal defect was reported in 13 patients (26.0%), ventricular septal defect in 9 (18.0%), coarctation of the aorta in 15 (30.0%), and patent ductus arteriosus in 13 (26.0%).

The 2 groups were not statistically significantly different vis-à-vis sex (P=0.785). The mean±SD of all the participants' age was 6.35±4.69 (range = 1-16) years, with the difference between the groups failing to constitute statistical significance

Table 1. Demographic characteristics of the study population*

Characteristic	Case (n=50)	Control (n=43)	P
Sex n (%)			0.785
Male	23 (52.3)	21 (47.7)	
Female	27 (55.1)	22 (44.9)	
Age (y)	5.81±4.21	6.98±5.18	0.470
Weight (kg)	23.50±15.22	28.27±18.24	0.285
Height (cm)	111.90±26.06	117.10±29.85	0.425
BMI	16.97±3.13	18.26±3.75	0.088
Systolic blood pressure	101.45±11.71	99.65±9.47	0.741
Diastolic blood pressure	68.54±6.18	56.69±7.20	0.101

*Data are presented as mean±SD or n (%).
BMI, Body mass index

Table 2. Clinical characteristics of participants*

Clinical Characteris-tic	Case (n=50)	Control (n=45)	Mean differ-ence	P	95% CI	
					Upper	Lower
CIMT (mm)	0.399±0.12	0.344±0.10	0.055	0.037	0.009	0.102
FMD	0.084±0.027	0.076±0.042	0.008	0.021	0.002	0.014

*Data are presented as mean±SD or n (%).
CIMT, Carotid intima-media thickness; FMD, Flow-mediated vasodilation

(P=0.470) (Table 1).

According to Table 2, the mean CIMT was significantly higher in the case group than in the control group (P=0.037). In addition, the mean FMD in the case group was higher than that of the control group (P=0.021). Nevertheless, the mean systolic and diastolic blood pressure was similar in both groups (Table 2).

The ROC curve for FMD, with an AUC of 0.640, showed that it could significantly indicate atherosclerosis changes in children with ACHD (95% CI, 0.525 to 0.754; P=0.021) (Figure 1). Further, the ROC curve for CIMT demonstrated that it could detect atherosclerosis early in children with ACHD (AUC, 0.626; 95% CI, 0.512 to 0.739; P=0.037) (Figure 2).

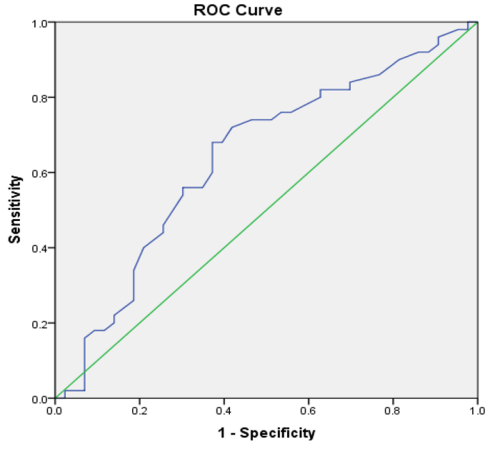

Figure 1. The image illustrates the FMD ROC curve to detect atherosclerosis early in children with ACHD.
FMD, Flow-mediated vasodilation; ROC, Receiver operating characteristic; ACHD, Acyanotic heart disease

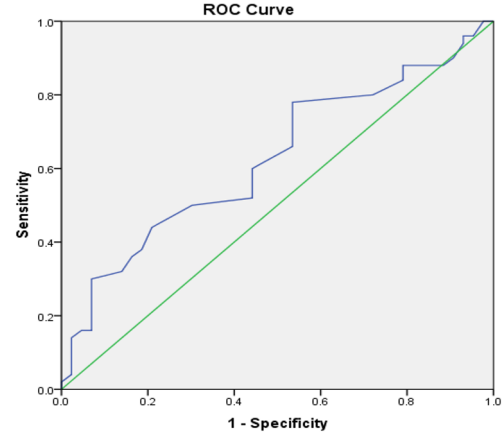

Figure 2. The image depicts the CIMT ROC curve to detect atherosclerosis early in children with ACHD.
CIMT, Carotid intima-media thickness; ROC, Receiver operating characteristic; ACHD, Acyanotic heart disease

Discussion

The principal finding of this present case-control research was the increase in CIMT and FMD in children with ACHD compared with healthy controls. Atherosclerosis is the precursor to coronary heart disease and stroke and is characterized by an accumulation of cholesterol-rich material in the arterial intimal-medial layers.[22] The CIMT of the common carotid artery, measured with high-resolution B-mode ultrasonography, is a useful noninvasive anatomic structural measure of cardiovascular disease.[22, 23] Moreover, CIMT is an excellent surrogate marker of macrovascular

atherosclerotic disease. It is widely used to study early structural changes in the arterial wall, including the endothelium, connective tissue, and smooth muscle.[22, 24]

Several studies have indicated that increased common CIMT is a more suitable indicator of generalized atherosclerosis and coronary artery disease than earlier methods.[3, 24-26] Meyer et al[27] showed that in patients with a history of coarctation of the aorta and repair, who were between 6 and 17 years old, CIMT was significantly higher than that in controls. Ayer et al[28] and Reiner et al[29] demonstrated that in children with a history of CHD, the average of CIMT was augmented, in line with our study.

Past investigations have suggested that factors related to atherosclerotic plaque progression (eg, VEGF, ET-1, iNOS, and HIF-1α) increased in patients with ACHD compared with controls.[30-33] CIMT is considered by the European Society of Pediatric Cardiology as a predictor of CVD among children and adolescents and can detect subclinical atherosclerosis, which was increased in our study. Consequently, patients with ACHD may be associated with the risk of atherosclerosis and endothelial dysfunction in the future.

The CIMT measurement in the current research differs from that in other studies. Duffels et al indicated that the mean CIMT was considerably decreased in adult cyanotic patients compared with controls.[34] In contrast, there was no difference in CIMT between adult cyanotic patients and healthy controls in the study by Trap et al.[35] Our results and those reported in previous studies are incompatible. What should be taken into consideration in this regard is the possible difference in the endothelial function in CHD patients with diverse age groups, warranting further research.

FMD is another noninvasive method with good validity and reasonable costs that indicates the diameter of the vessel wall due to changes in blood flow and is proposed as another predictor for CVD among children and adolescents.[6, 21-32] Evaluation of the endothelial function with FMD is as valuable as the invasive tests of coronary arteries and the assessment of the presence and severity of coronary atherosclerosis.[36, 37]

Liao et al[38] reported that in children with postural orthostatic tachycardia syndrome, FMD was significantly increased, similar to our study. Nevertheless, in contrast to our findings, 2 prior studies reported remarkably lower FMD in adult cyanotic CHD.[39, 40] Çiftel et al[41] indicated that in children with irreversible pulmonary hypertension due to CHD, the mean FMD was decreased compared with healthy subjects.

Other investigations have reported no difference concerning FMD changes between adults with cyanotic CHD and controls. Still, it is noteworthy that changes in age, disease type, and the measurement method may affect the results of FMD.

In the current study, we assessed the performance of FMD and CIMT. According to ACU, the performance of FMD and CIMT was poor but meaningful.

Conclusion

In children with ACHD, FMD and CIMT measurements improved cardiovascular risk assessment. CIMT and FMD were significantly increased, which may be a predictive factor for atherosclerosis risk in patients with ACHD. Further research in this regard is recommended.

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References

1. Mayhew AJ, de Souza RJ, Meyre D, Anand SS, Mente A. A systematic review and meta-analysis of nut consumption and incident risk of CVD and all-cause mortality. Br J Nutr 2016;115:212-225.
2. Candelino M, Tagi VM, Chiarelli F. Cardiovascular risk in children: a burden for future generations. Ital J Pediatr 2022;48:57.
3. Naqvi TZ, Lee MS. Carotid intima-media thickness and plaque in cardiovascular risk assessment. JACC Cardiovasc Imaging 2014;7:1025-1038.
4. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. JAMA 2004;291:210-215.
5. Sabri MR, Tavana EN, Ahmadi A, Gheissari A. Effect of vitamin C on endothelial function of children with chronic renal failure: An experimental study. Adv Biomed Res 2015;4:260.
6. Dalla Pozza R, Ehringer-Schetitska D, Fritsch P, Jokinen E, Petropoulos A, Oberhoffer R; Association for European Paediatric Cardiology Working Group Cardiovascular Prevention. Intima media thickness measurement in children: A statement from the Association for European Paediatric Cardiology (AEPC) Working Group on Cardiovascular Prevention endorsed by the Association for European Paediatric Cardiology. Atherosclerosis 2015;238:380-387.
7. Rohit M, Shrivastava S. Acyanotic and Cyanotic Congenital Heart Diseases. Indian J Pediatr 2018;85:454-460.
8. Moller JH, Hoffman J IE, Benson DW, Van Hare GF, Wren C, eds. Pediatric Cardiovascular Medicine. 7th ed. Pondicherry: Wiley-Blackwell; 2012. p. 23–32.
9. Hoffman JI, Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol 2002;39:1890-900.
10. Ahmadi AR, Sabri MR, Navabi ZS, Ghaderian M, Dehghan B, Mahdavi C, Khodarahmi S. Early Results of the Persian Registry of Cardiovascular Disease/Congenital Heart Disease (PROVE/CHD) in Isfahan. J Tehran Heart Cent 2020;15:158-164.
11. Khasawneh W, Hakim F, Abu Ras O, Hejazi Y, Abu-Aqoulah A. Incidence and Patterns of Congenital Heart Disease Among Jordanian Infants, a Cohort Study From a University Tertiary Center. Front Pediatr 2020;8:219.
12. Wallooppillai NJ, Jayasinghe Mde S. Congenital heart disease in Ceylon. Br Heart J 1970;32:304-306.

13. van der Linde D, Konings EE, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJ, Roos-Hesselink JW. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. J Am Coll Cardiol 2011;58:2241-2247.
14. Ross R. Atherosclerosis--an inflammatory disease. N Engl J Med 1999;340:115-126.
15. Celermajer DS, Sorensen KE, Gooch VM, Spiegelhalter DJ, Miller OI, Sullivan ID, Lloyd JK, Deanfield JE. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. Lancet 1992;340:1111-1115.
16. Sabri MR, Tavana EN, Ahmadi A, Hashemipour M. The effect of vitamin C on endothelial function of children with type 1 diabetes: an experimental study. Int J Prev Med 2014;5:999-1004.
17. Raitakari OT, Juonala M, Kähönen M, Taittonen L, Laitinen T, Mäki-Torkko N, Järvisalo MJ, Uhari M, Jokinen E, Rönnemaa T, Akerblom HK, Viikari JS. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. JAMA 2003;290:2277-2283.
18. Burke GL, Evans GW, Riley WA, Sharrett AR, Howard G, Barnes RW, Rosamond W, Crow RS, Rautaharju PM, Heiss G. Arterial wall thickness is associated with prevalent cardiovascular disease in middle-aged adults. The Atherosclerosis Risk in Communities (ARIC) Study. Stroke 1995;26:386-391.
19. Brunner H, Cockcroft JR, Deanfield J, Donald A, Ferrannini E, Halcox J, Kiowski W, Lüscher TF, Mancia G, Natali A, Oliver JJ, Pessina AC, Rizzoni D, Rossi GP, Salvetti A, Spieker LE, Taddei S, Webb DJ; Working Group on Endothelins and Endothelial Factors of the European Society of Hypertension. Endothelial function and dysfunction. Part II: Association with cardiovascular risk factors and diseases. A statement by the Working Group on Endothelins and Endothelial Factors of the European Society of Hypertension. J Hypertens 2005;23:233-246.
20. Sabri MR, Tavana EN, Ahmadi A, Mostafavy N. Does Vitamin C improve endothelial function in patients with Kawasaki disease? J Res Med Sci 2015;20:32-36.
21. Sorensen KE, Celermajer DS, Spiegelhalter DJ, Georgakopoulos D, Robinson J, Thomas O, Deanfield JE. Non-invasive measurement of human endothelium dependent arterial responses: accuracy and reproducibility. Br Heart J 1995;74:247-253.
22. Falk E. Pathogenesis of atherosclerosis. J Am Coll Cardiol 2006;47(8 Suppl):C7-12.
23. Bis JC, Kavousi M, Franceschini N, Isaacs A, Abecasis GR, Schminke U, Post WS, Smith AV, Cupples LA, Markus HS, Schmidt R, Huffman JE, Lehtimäki T, Baumert J, Münzel T, Heckbert SR, Dehghan A, North K, Oostra B, Bevan S, Stoegerer EM, Hayward C, Raitakari O, Meisinger C, Schillert A, Sanna S, Völzke H, Cheng YC, Thorsson B, Fox CS, Rice K, Rivadeneira F, Nambi V, Halperin E, Petrovic KE, Peltonen L, Wichmann HE, Schnabel RB, Dörr M, Parsa A, Aspelund T, Demissie S, Kathiresan S, Reilly MP, Taylor K, Uitterlinden A, Couper DJ, Sitzer M, Kähönen M, Illig T, Wild PS, Orru M, Lüdemann J, Shuldiner AR, Eiriksdottir G, White CC, Rotter JI, Hofman A, Seissler J, Zeller T, Usala G, Ernst F, Launer LJ, D'Agostino RB Sr, O'Leary DH, Ballantyne C, Thiery J, Ziegler A, Lakatta EG, Chilukoti RK, Harris TB, Wolf PA, Psaty BM, Polak JF, Li X, Rathmann W, Uda M, Boerwinkle E, Klopp N, Schmidt H, Wilson JF, Viikari J, Koenig W, Blankenberg S, Newman AB, Witteman J, Heiss G, Duijn Cv, Scuteri A, Homuth G, Mitchell BD, Gudnason V, O'Donnell CJ; CARDIoGRAM Consortium. Meta-analysis of genome-wide association studies from the CHARGE consortium identifies common variants associated with carotid intima media thickness and plaque. Nat Genet 2011;43(10):940-947.
24. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. Circulation 2007;115:459-467.
25. Melton PE, Carless MA, Curran JE, Dyer TD, Göring HH, Kent JW Jr, Drigalenko E, Johnson MP, Maccluer JW, Moses EK, Comuzzie AG, Mahaney MC, O'Leary DH, Blangero J, Almasy L. Genetic architecture of carotid artery intima-media thickness in Mexican Americans. Circ Cardiovasc Genet 2013;6:211-221.
26. Nambi V, Chambless L, Folsom AR, He M, Hu Y, Mosley T, Volcik K, Boerwinkle E, Ballantyne CM. Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: the ARIC (Atherosclerosis Risk In Communities) study. J Am Coll Cardiol 2010;55:1600-1607.
27. Meyer AA, Joharchi MS, Kundt G, Schuff-Werner P, Steinhoff G, Kienast W. Predicting the risk of early atherosclerotic disease development in children after repair of aortic coarctation. Eur Heart J 2005;26:617-622.
28. Ayer JG, Harmer JA, Nakhla S, Xuan W, Ng MK, Raitakari OT, Marks GB, Celermajer DS. HDL-cholesterol, blood pressure, and asymmetric dimethylarginine are significantly associated with arterial wall thickness in children. Arterioscler Thromb Vasc Biol 2009;29:943-949.
29. Reiner B, Oberhoffer R, Häcker AL, Ewert P, Müller J. Carotid Intima-Media Thickness in Children and Adolescents With Congenital Heart Disease. Can J Cardiol 2018;34:1618-1623.
30. El-Melegy NT, Mohamed NA. Angiogenic biomarkers in children with congenital heart disease: possible implications. Ital J Pediatr 2010;36:32.
31. Celletti FL, Waugh JM, Amabile PG, Brendolan A, Hilfiker PR, Dake MD. Vascular endothelial growth factor enhances atherosclerotic plaque progression. Nat Med 2001;7:425-429.
32. Yin HL, Luo CW, Dai ZK, Shaw KP, Chai CY, Wu CC. Hypoxia-inducible factor-1α, vascular endothelial growth factor, inducible nitric oxide synthase, and endothelin-1 expression correlates with angiogenesis in congenital heart disease. Kaohsiung J Med Sci 2016;32:348-55.
33. Nassef YE, Hamed MA, Aly HF. Inflammatory cytokines, apoptotic, tissue injury and remodeling biomarkers in children with congenital heart disease. Indian J Clin Biochem 2014;29:145-149.
34. Mayyas F, Niebauer M, Zurick A, Barnard J, Gillinov AM, Chung MK, Van Wagoner DR. Association of left atrial endothelin-1 with atrial rhythm, size, and fibrosis in patients with structural heart disease. Circ Arrhythm Electrophysiol 2010;3:369-379.
35. Tarp JB, Sørgaard MH, Christoffersen C, Jensen AS, Sillesen H, Celermajer D, Eriksson P, Estensen ME, Nagy E, Holstein-Rathlou NH, Engstrøm T, Søndergaard L. Subclinical atherosclerosis in patients with cyanotic congenital heart disease. Int J Cardiol 2019;277:97-103.
36. Joannides R, Haefeli WE, Linder L, Richard V, Bakkali EH, Thuillez C, Lüscher TF. Nitric oxide is responsible for flow-dependent dilatation of human peripheral conduit arteries in vivo. Circulation 1995;91:1314-1319.
37. Takase B, Uehata A, Akima T, Nagai T, Nishioka T, Hamabe A, Satomura K, Ohsuzu F, Kurita A. Endothelium-dependent flow-mediated vasodilation in coronary and brachial arteries in suspected coronary artery disease. Am J Cardiol 1998;82:1535-1539, A7-8.
38. Liao Y, Chen S, Liu X, Zhang Q, Ai Y, Wang Y, Jin H, Tang C, Du J. Flow-mediated vasodilation and endothelium function in children with postural orthostatic tachycardia syndrome. Am J Cardiol 2010;106:378-382.
39. Trojnarska O, Szczepaniak-Chicheł L, Gabriel M, Bartczak-Rutkowska A, Rupa-Matysek J, Tykarski A, Grajek S. Arterial stiffness and arterial function in adult cyanotic patients with congenital heart disease. J Cardiol 2017;70:62-67.
40. Cordina RL, Nakhla S, O'Meagher S, Leaney J, Graham S, Celermajer DS. Widespread endotheliopathy in adults with cyanotic congenital heart disease. Cardiol Young 2015;25:511-519.
41. Ciftel M, Simşek A, Turan O, Kardelen F, Akçurin G, Ertuğ H. Endothelial dysfunction and atherosclerosis in children with irreversible pulmonary hypertension due to congenital heart disease. Ann Pediatr Cardiol 2012;5:160-164.