İnvestigation of endothelial dysfunction in children with acute rheumatic fever

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ABSTRACT

Background : **Acute rheumatic fever (ARF) is an important cause of valvular heart disease in children. Endothelial dysfunction plays an important role in the pathogenesis of valvular heart diseases. The role of endothelial dysfunction in valvular heart diseases due to ARF is not exactly known. In ARF, autoimmune injury, inflammation, oxidative stress, and impairment of nitric oxide in valvular endothelium may be the causes of endothelial dysfunction. The purpose of this study is to evaluate endothelial dysfunction and arterial stiffness in children with ARF.**

Materials and Methods : **Thirty-six patients diagnosed with ARF (the mean age was 11.80 ± 2.82 years) and 36 volunteered individuals with similar age, sex, and body mass index were included in the study. The study groups were compared in terms of M-mode echocardiography parameters, carotid arterial strain (CAS), beta-stiffness index (βSI), and flow-mediated dilation (FMD).**

Results : **In patients with ARF, there was a decrease in FMD% (10.36 ± 7.26 and 12.76 ± 4.59; $P < 0.001$) compared to the control group. In addition, CAS (0.16 ± 0.06 and 0.18 ± 0.08; $P = 0.44$) and βSI (3.65 ± 1.61 and 3.57 ± 2.38; $P = 0.24$) were similar in the patient and the control groups. Furthermore, no correlation was detected between decreased FMD value and mitral regurgitation ($r = -0.07$; $P = 0.66$), aortic regurgitation ($r = -0.04$; $P = 0.78$), CAS ($r = -0.08$; $P = 0.61$), and βSİ ($r = -0.20$; $P = 0.22$).**

Conclusion : **In our study, a decrease in FMD value, which is a marker of endothelial dysfunction, was found in children with rheumatic carditis.**

Keywords : Acute rheumatic fever, arterial stiffness, endothelial dysfunction, flow-mediated dilatation

INTRODUCTION

Acute rheumatic fever (ARF) is an autoimmune disease that occurs as a result of Group A streptococcus infection. It arises principally as a childhood disease. While its frequency decreases in developed countries, it is an important cause of valvular heart disease in developing countries.[1] ARF causes rheumatic heart disease by inducing an unfavorable effect, especially on the cardiovascular system. The damage that occurs on cardiac valves is presumed to be the result of an autoimmune response. However, the exact mechanism

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is yet to be totally understood. Endothelial damage has recently become prominent in the pathogenesis of rheumatic carditis.[2] Humoral immunity induced by streptococcus infection causes initial endothelial damage. As a result of endothelial dysfunction, adhesion molecules are expressed from the endothelium, cellular immunity becomes activated, and lymphocytes and macrophages penetrate the valvular tissue causing damage.[1-4]

Endothelium is the inner cellular lining of blood vessels and lymphatic system. Therefore, endothelium is in direct relationship with blood, lymph, and other circulating cells. It has an important role in vascular and valvular structures. Endothelium has important functions such as the regulation of vascular tone, vascular remodeling, regulation of immunity, inflammation, platelet aggregation, and in the steps of thrombosis and angiogenesis. Endothelial dysfunction can develop through mechanical strain, bacterial infection, inflammation, and autoantibodies. Endothelial dysfunction has an important role in valvular heart disease, atherosclerosis, mitral valve prolapse, and infective endocarditis.[3]

In patients with ARF, inflammation, autoimmune injury to the valvular endothelium, oxidative stress, decreased antioxidant capacity, deterioration of nitric oxide (NO) metabolism, and increase in endothelin 1 and adhesion molecules may result in endothelial dysfunction.[3-8] In addition, serum asymmetric dimethylarginine (ADMA) levels were found to increase in late period in patients with ARF. Increase in ADMA results in decreased endothelial NO synthase activity and inhibits NO production from arginine.[9,10] NO has an important role in the regulation of vascular tone and local blood flow. Decreased NO production or bioactivity leads to endothelial dysfunction.[3,10] Flow-mediated dilatation (FMD) is the most commonly used method in the detection of endothelial dysfunction. FMD of the brachial artery is an accepted method for noninvasive assessment of systemic endothelial function and endothelium dependent vasodilatory response of a vessel to elevations in blood flow-associated shear stress.[11]

The purpose of this study is to evaluate endothelial dysfunction and arterial stiffness in children with ARF.

MATERIALS AND METHODS

Study population

The study had a cross-sectional design. The study was initiated upon approval from the hospital ethics committee. Patients diagnosed with ARF at Sanliurfa Training and Research Hospital Pediatric Cardiology Outpatient Clinic between February 2016 and June 2017 were included in the study. Patients with rheumatic carditis aged between 7 and 16 years were included in the study for optimal ultrasound imaging. The diagnosis of all the patients included in the study was made according to the 2015 Revised Jones Criteria for ARF.[12] 36 patients with ARF (20 males and 16 females) and a control group of 36 healthy controls (20 males and 16 females) were included in the study. ARF patients without a diagnosis of carditis were excluded from the study. In addition, patients with hypertension, diabetes mellitus, hypercholesterolemia, mitral stenosis, and obesity were excluded from the study.

Among patients with rheumatic carditis, there were 34 patients with mitral regurgitation (MR) and 20 patients with aortic regurgitation (AR). Grade 1 MR was seen in 12 patients, Grade 2 MR in 8 patients, Grade 3 MR in 8 patients, and Grade 4 MR in 6 patients. MR was not detected in 2 of the patients. Grade 1 AR was seen in 8 patients, Grade 2 AR in 5 patients, Grade 3 AR in 4 patients, and Grade 4 AR in 3 patients.

Measurements for weight, height, systolic blood pressure (SBP), and diastolic blood pressure (DBP), all echocardiographic measurements, carotid artery diameter measurements, brachial artery diameter measurements, and FMD were performed after ARF diagnosis and before treatment (benzathine penicillin G, anticongestive treatment, aspirin, or steroid according to the degree of carditis).

Echocardiographic examination

In all cases, two-dimensional, M-mode, pulsed, and color flow Doppler echocardiographic examinations (Vivid 7 pro, GE, Horten, Norway, 3 MHz transducer) were performed by a cardiologist who was blinded to the clinical details and results of the other investigations of each patient and control. During echocardiography, a 1-lead electrocardiography was recorded continuously. The systolic function of the left ventricle was evaluated using M-mode echocardiography in the parasternal long-axis view.[13] Left atrial dimension determined by M-mode echocardiography was assessed in a plane parallel to the mitral valve annulus in the parasternal long-axis view during atrial end diastole.[14]

The mitral insufficiency and aortic insufficiency detected with color Doppler in patients with ARF were performed based on the measurement of jet length. This value was considered as Grade 1 when it was equal to or below 1.5 cm, as Grade 2 when it was between 1.5 and 2.9 cm, as Grade 3 when it was between 3.0 and 4.4 cm, and as Grade 4 when it was above 4.5 cm. Grade 1 was accepted as mild insufficiency, Grade 2 was accepted as moderate, and Grade 3 and 4 were accepted as severe insufficiency.[15]

The World Health Organization recommends the following

criteria to differentiate pathologic from physiologic mitral and aortic regurgitation: (a) color jet longer than 1 cm, (b) color jet evident in at least two imaging planes, (c) color jet mosaic with peak velocity >2.5 m/s, and (d) Doppler signal holosystolic for mitral regurgitation and holodiastolic for aortic regurgitation.[16] Pathological valvular insufficiencies were evaluated in accordance with the World Health Organization recommendation.

Arterial stiffness measurement

Blood pressure measurement: All cases rested in the supine position for 15 min and then their right brachial artery pressure was measured by sphygmomanometer with appropriate cuff. Both SBP and DBP were measured, and after three measurements, the mean value was obtained.

High-resolution B-mode ultrasound imaging of the carotid arteries was performed using a GE scanner (with a 12-MHz transducer; Vivid 7 GE Vingmed, Horten, Norway) with patients in the supine position. The best acoustic window was identified with the jugular vein above the common carotid artery and a series of images were acquired over a 20 s period. Five to six cardiac cycles on average were used for the estimation of carotid diameters. Carotid arterial strain (CAS) and beta-stiffness index (βSI) were calculated by echocardiographic measurements. CAS as (Ds – Dd)/Dd and stiffness as βSI = ln (SBP/DBP)/ strain, where SBP is systolic blood pressure, DBP is diastolic blood pressure, Ds is arterial systolic diameter, and Dd is arterial diastolic diameter.[17,18]

Flow-mediated dilatation measurement

Patients were advised to stop drinking coffee, smoking, drinking alcohol, and exercising at least 8 h before the procedure, even though they were in the pediatric age group. All cases rested for at least 15 min in a supine position in a quiet, dark, air-conditioned room before any measurement. The brachial artery diameter was measured in the antecubital fossa just before it divided into branches using a Doppler ultrasound system with a high-resolution 12-MHz linear array transducer (with a 12-MHz transducer; Vivid 7 GE Vingmed, Horten, Norway). For two-dimensional imaging, a segment with clearly identifiable anterior and posterior intimal faces was selected. The brachial artery diameter was measured three times and the average of these three measurements was recorded as the basal diameter. These measurements taken from the brachial artery were taken at the end of diastole according to electrocardiography monitoring. The cuff of the blood pressure device was placed in the upper part of the right antecubital fossa to create current impulses in the brachial artery. After baseline measurements were recorded, the cuff pressure was increased to 50 mmHg above the SBP of the patient and the cuff was held in this position for 5 min to allow complete interruption of arterial flow. Anterograde blood flow was cut and ischemia was induced. After the cuff was deflated, 2D images of the brachial artery at longitudinal section were taken at 60th second. FMD values were calculated using baseline diameter, and the maximum diameter of the brachial artery obtained from these measurements FMD was calculated according to this formula: FMD = 100 × (maximum diameter after hyperemia – baseline diameter/baseline diameter).[11,19]

Statistical analysis

SPSS 17.0 statistical program (SPSS Inc., Chicago, IL, USA) was used for statistical study. All values are given as median, means plus or minus the standard deviations. Pearson's Chi-square was used for gender, and the normal distribution test, Shapiro–Wilk test, was performed for all other variables. The nonparametric test, Mann–Whitney U-test, was performed when variables did not comply with normal distribution. Spearman's correlation analysis was used for the correlations. $P < 0.05$ was considered statistically significant.

RESULTS

Clinical characteristics and M-mode echocardiographic findings were compared between the patient and control groups [Table 1]. When AFR patients and control groups were compared in terms of clinical features, age, body mass index, SBP, and DBP were found to be similar. In addition, when the two groups were compared in terms of echocardiographic findings, diastolic interventricular septal wall thickness and diastolic left ventricular posterior wall thickness were found to be similar ($P > 0.05$). However, the left ventricular end-diastolic diameter, left ventricular end-systolic diameter, systolic left ventricular posterior wall thickness, systolic interventricular septal wall thickness, and left atrial diameter were significantly increased in patients with ARF ($P < 0.05$).

FMD and carotid artery stiffness parameters (CAS and βSİ) were compared between the patient and control groups [Table 2]. In patients with ARF, there was a decrease in FMD% (10.36 ± 7.26 and 12.76 ± 4.59; $P < 0.001$) compared to the control group. However, in patients with ARF, CAS (0.16 ± 0.06 and 0.18 ± 0.08; $P = 0.44$) and βSİ (3.65 ± 1.61 and 3.57 ± 2.38; $P = 0.24$) were found to be similar to the control group.

In correlation analysis, no correlation was detected between FMD value and MR ($r = –0.07$; $P = 0.66$), AR ($r = –0.04$; $P = 0.78$), CAS ($r = –0.08$; $P = 0.61$), and βSİ ($r = –0.20$; $P = 0.22$) ($P > 0.05$).

DISCUSSION

ARF occurs as a result of complex interactions between Group A streptococcus, a susceptible host, and the environment. An abnormal immune response

Table 1: Clinical characteristics and M-mode echocardiographic parameters

	ARF (36 patients)	Controls (36 subjects)	*P*
Age (years)	11.80±2.82	11.72±2.80	0.90
BMI (kg/m^2)	20.80±1.92	20.36±1.85	0.57
SBP (mmHg)	109.86±6.07	108.38±6.70	0.39
DBP (mmHg)	65.44±6.42	67.25±5.25	0.18
IVSd (mm)	9.27±1.92	8.88±1.89	0.32
LVIDd (mm)	46.36± 6.69	38.47±5.10	<0.001
LVPWd (mm)	8.50±1.10	8.22±2.16	0.38
IVSs (mm)	12.69±2.16	11.86±1.82	0.02
LVIDs (mm)	28.58±4.56	22.97±4.32	<0.001
LVPWs (mm)	13.30±1.68	12.27± 2.39	<0.05
EF	65.63±6.04	70.72±7.46	<0.05
LA diameter (mm)	31.80±6.55	27.875±4.17	<0.05

BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, IVSd: İnterventricular septal wall thickness (diastolic), LVIDd: Left ventricular internal dimension (diastolic), LVPWd: Left ventricular posterior wall thickness (diastolic), IVSs: İnterventricular septal wall thickness (systolic) LVIDs: Left ventricular internal dimension (systolic), LVPWs: Left ventricular posterior wall thickness (systolic), EF: Ejection fraction LA: Left atrium, ARF: Acute rheumatic fever

Table 2: Brachial artery measurement, flow-mediated dilatation, and carotid artery stiffness results

	ARF (36 patients)	Controls (36 subjects)	*P*
BABd (mm)	3.29±0.38	3.28±0.36	0.77
BAD1m (mm)	3.62±0.40	3.71±0.42	<0.001
FMD (%)	10.36±7.26	12.76±4.59	<0.001
Ds (mm)	5.16±0.74	5.15±0.80	0.86
Dd (mm)	4.39±0.73	4.36±0.75	0.99
CAS	0.16±0.06	0.18±0.08	0.44
βSİ	3.65±1.61	3.57±2.38	0.24

BABd: Brachial artery basal diameter, BAD1m: Brachial artery diameter in the 1st Min FMD: Flow-mediated dilatation. Ds: Carotid systolic diameter, Dd: Carotid diastolic diameter, CAS: Carotid arterial strain, βSİ: Beta-stiffness index

leads to an acute inflammatory illness that most commonly affects the joints, brain, and heart. The most important finding in ARF is mitral and aortic valve failure.[1,12] Endothelial damage has recently become prominent in the pathogenesis of rheumatic carditis. The resulting antigens and superantigens of Group A streptococcus infection activate B and T lymphocytes, leading to increased cytokines and cross-reactive autoantibodies. Cross-reactive antibodies are attached to the valvular endothelium and cause inflammation in the endothelial layer. Adhesion molecules are expressed from dysfunctional endothelium. Adhesion molecules cause adhesion of leukocytes to the endothelium and extravasation of the leukocytes.[2,20] This lymphocytic penetration causes certain changes even dysfunction of the endothelial cells, which may result in the initiation of valve injuries during rheumatic carditis. Endothelial dysfunction is a valvular heart disease which plays an important role in pathogenesis. Heart valve remodeling occurs due to endothelial dysfunction and regurgitation or stenosis may develop due to impairment in the structure of cardiac valve.[2,20,21] The data suggest that the mechanism of pathogenesis in rheumatic carditis begins at the valve surface endothelium.[4,20,21]

Endothelium has important functions such as the regulation of vascular tonus, vascular remodeling, regulation of immunology, inflammation, platelet aggregation, and in the steps of thrombosis and angiogenesis. It has become increasingly evident that the endothelium plays a critical role in the pathogenesis of valvular heart disease. Endothelial dysfunction in valvular heart disease occurs due to mechanical forces, bacterial infection, inflammation, and autoantibodies in circulation.[3]

In rheumatic carditis, impairments were detected in various markers that can indicate endothelial dysfunction. In rheumatic carditis, levels of pro-inflammatory cytokines and NO increase.[8,22] Inflammation-triggered release of cytokines induced NO production that mediates endothelial dysfunction.[22,23] NO level increase might be playing a significant role in myocardial contractile dysfunction and alteration of vascular response of cardiac failure.[24] NO plays an important regulatory and modulatory role in a variety of inflammatory conditions. It is an important mediator of immunity and inflammation. The increase in inflammation and cytokines in the endothelial layer during rheumatic carditis activates the NOS enzyme and results in an increase in NO levels. Increased levels of NO are indicative of NO endothelial dysfunction.[7] In addition, endothelial microparticles (EMPs), a marker of endothelial dysfunction, were found to be high in rheumatic carditis.[25,26] EMPs were subcellular fragments of the endothelial cell lipid bilayer and shed from endothelial cells by a variety of stimuli to activate endothelial cells. Furthermore, EMP may play an important role in inflammation, coagulation, vascular dysfunction, and angiogenesis. Mitral valve stenosis or regurgitation leading to the turbulent flow can induce hemodynamic changes and shear stress, which may result in the activated or injured endothelium. The increase in EMP can, in turn, impair mitral valve endothelial cells by reducing NO production and increasing free O_2 through inhibiting the endothelial NO synthase signaling pathway; EMP causes endothelial dysfunction in the cardiac valves and increased EMP is associated with the severity of heart failure.[25] Oxidative stress and reduced antioxidant capacity in ARF patients is another cause of endothelial dysfunction.[5] Adhesion molecules are biomarkers for endothelial function and have important roles in the immune system. Increases in intercellular adhesion molecules, vascular cell adhesion molecules, and endothelial selectin levels were detected rheumatic cardiac. The increase in the adhesion molecules is associated with valvular damage and endothelial dysfunction.[21,23] A variety of biomarkers have been identified that are indicative of endothelial dysfunction

in rheumatic carditis.[7,8,21-26] However, the presence of endothelial dysfunction in rheumatic carditis has not been studied clinically. FMD is the most commonly used method in the diagnosis of endothelial dysfunction clinically. FMD of the brachial artery is an accepted method for noninvasive assessment of systemic endothelial function. The shear stress that occurs during the test results in vasodilatation, which results in NO production.[11]

We studied arterial stiffness and endothelial dysfunction in patients with rheumatic carditis. In our study, we found a decrease in FMD in patients with rheumatic carditis. Decrease in FMD is an indicator of endothelial dysfunction. Studies on endothelial dysfunction and its importance in ARF patients are limited. Recently, the focus has been on endothelial dysfunction in patients with rheumatic carditis, but there has been no study that reveals this clinically. Previous limited studies have demonstrated impairment of NO production associated with rheumatic carditis, increased EMP, oxidative stress, decreased antioxidant capacity, and increased adhesion molecules in rheumatic carditis.[7,8,21-26] In addition, an increase in the level of ADMA was detected in the late period of rheumatic carditis. Increase in ADMA results in decreased endothelial NO synthase activity and inhibits NO production from arginine.[9,10] NO has important role in the regulation of vascular tone and local blood flow. Decreased NO production or bioactivity causes endothelial dysfunction.[27] In patients with chronic rheumatic carditis, increased arterial stiffness values were found especially due to continuing inflammation.[28] We found similar arterial stiffness parameters in patients with rheumatic carditis and the control group during the acute period of the illness.

CONCLUSION

We found a decrease in FMD value in patients with rheumatic carditis. Decreased FMD is an indicator of endothelial dysfunction. In addition, we did not detect any abnormality in arterial stiffness parameters in patients with rheumatic carditis. More comprehensive studies are needed to establish endothelial dysfunction and its importance in rheumatic carditis and to target endothelial dysfunction therapeutically.

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Conflicts of interest

There are no conflicts of interest.

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