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 of endothelial dysfunction is not fully understood. 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.

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is yet to be totally understood. Endothelial damage has recently become prominent in the pathogenesis of rheumatic carditis.\cite{1} 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.\cite{2,3}

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.\cite{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.\cite{4,5} 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.\cite{6} NO has an important role in the regulation of vascular tone and local blood flow. Decreased NO production or bioactivity leads to endothelial dysfunction.\cite{7,8} 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.\cite{9}

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.\cite{10} 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.\cite{11} 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.\cite{12}

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.\cite{13}

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. 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.

**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: \( FMD = 100 \times \frac{\text{maximum diameter after hyperemia} - \text{baseline diameter}}{\text{baseline diameter}} \). 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–Wilks 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 βSI) were compared between the patient and control groups [Table 2]. In patients with ARF, there was a decrease in FMD% \( (10.36 \pm 7.26 \text{ and } 12.76 \pm 4.59; P < 0.001) \) compared to the control group. However, in patients with ARF, CAS \( (0.16 \pm 0.06 \text{ and } 0.18 \pm 0.08; P = 0.44) \) and βSI \( (3.65 \pm 1.61 \text{ and } 3.57 \pm 2.38; P = 0.24) \) 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 βSI \( (r = -0.20; P = 0.22; P > 0.05) \).

**DISCUSSION**

ARF occurs as a result of complex interactions between Group A streptococcus, a susceptible host, and the environment. An abnormal immune response...
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.\cite{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 leucocytes to the endothelium and extravasation of the leukocytes.\cite{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.\cite{2,20,21} The data suggest that the mechanism of pathogenesis in rheumatic carditis begins at the valve surface endothelium.\cite{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.\cite{5}

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.\cite{8,21} Inflammation-triggered release of cytokines induced NO production that mediates endothelial dysfunction.\cite{22,23} NO level increase might be playing a significant role in myocardial contractile dysfunction and alteration of vascular response of cardiac failure.\cite{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.\cite{7} In addition, endothelial microparticles (EMPs), a marker of endothelial dysfunction, were found to be high in rheumatic carditis.\cite{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.\cite{25} Oxidative stress and reduced antioxidant capacity in ARF patients is another cause of endothelial dysfunction.\cite{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 carditic. The increase in the adhesion molecules is associated with valvular damage and endothelial dysfunction.\cite{21,23} A variety of biomarkers have been identified that are indicative of endothelial dysfunction.

### 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)        | 12.89±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        | 27.87±4.17             | <0.05|

BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, IVSd: Interventricular septal wall thickness (diastolic), LVIDd: Left ventricular internal dimension (diastolic), LVPWd: Left ventricular posterior wall thickness (diastolic), IVSs: Interventricular 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         | 4.38±0.75              | 0.99|
| CAS              | 0.16±0.06         | 0.18±0.08              | 0.44|
| iSI              | 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, iSI: Beta-stiffness index
in rheumatic carditis. 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.

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. 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. NO has important role in the regulation of vascular tone and local blood flow. Decreased NO production or bioactivity causes endothelial dysfunction. In patients with chronic rheumatic carditis, increased arterial stiffness values were found especially due to continuing inflammation.

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.

REFERENCES

1. Marijon E, Mirabel M, Celermajer DS, Jouven X. Rheumatic heart disease. Lancet 2012;379:953-64.
2. Tandon R. Rheumatic fever pathogenesis: Approach in research needs change. Ann Pediatr Cardiol 2012;5:169-78.
3. Leask RL, Jain N, Butany J. Endothelium and valvular diseases of the heart. Microsc Res Tech 2003;60:129-37.
4. Roberts S, Kosanke S, Terrence Dunn S, Jankelow D, Duran CM, Cunningham MW. Pathogenic mechanisms in rheumatic carditis: Focus on valvular endothelium. J Infect Dis 2001;183:507-11.
5. Uner A, Sal E, Doğan M, Sanlı FM, Acikgoz M, Cemek M, et al. Investigation of oxidant and antioxidant pathway changes in acute rheumatic fever. Acta Cardiol 2010;65:53-7.
6. Kuran S, Mehmetoglu I, Oran B, Kiyici A. Homocysteine levels and total antioxidant capacity in children with acute rheumatic fever. Clin Biochem 2008;41:26-9.
7. Balat A, Kiliç M, Cekmen MB, Güler E, Yürekli M, Sahinöz S, et al. Adrenomedullin and total nitrite levels in children with acute rheumatic fever. Clin Biochem 2005;38:526-30.
8. Narin F, Narin N, Pasaoğlu H, Halici C, Aslan D. Nitric oxide metabolites in acute rheumatic fever. Tohoku J Exp Med 2003;199:135-9.
9. Sert A, Cimen D, Arslan D. Serum asymmetric dimethylarginine levels in patients with acute rheumatic fever. J Pediatr Biochem 2015;5:21-7.
10. Sibal L, Agarwal SC, Home PD, Boger RH. The role of asymmetric dimethylarginine (ADMA) in endothelial dysfunction and cardiovascular disease. Curr Cardiol Rev 2010;6:82-90.
11. Charakida M, Masi S, Lüscher TF, Kastelein JJ, Deanfield JE. Assessment of atherosclerosis: The role of flow-mediated dilatation Eur Heart J 2010;31:2854-61.
12. Gewitz MH, Baltimore RS, Tani LY, Sable CA, Shulman ST, Carapetis J, et al. American heart association committee on rheumatic fever, endocarditis, and Kawasaki disease of the council on cardiovascular disease in the young. Revision of the Jones Criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: A scientific statement from the American Heart Association. Circulation 2015;131:1806-18.
13. Kimball TR, Michelfelder EC. Echocardiography. In: Allen HD, Driscoll DJ, Shaddy RE, Feltes TF, editors. Moss and Adams’ Heart Disease in Infants, Children, and Adolescents: Including the Fetus and Young Adult. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2008. p. 95-163.
14. Patel VV, Ren JF, Marchlinski FE. A comparison of left atrial size by two-dimensional transthoracic echocardiography and magnetic endocardial catheter mapping. Pacing Clin Electrophysiol 2002;25:95-7.
15. Otto CM. Valvular regurgitation: Diagnosis quantitation and clinical approach. In: Text Book of Clinical Echocardiography, 2nd ed. Washington: Saunders Company; 2000. p. 265-300.
16. Rheumatic fever and rheumatic heart disease. World Health Organ Tech Rep Ser 2004;923:1-122, back cover.
17. Gürses D, Ozyürek AR, Levent E, Ulger Z. Elastic...
properties of the abdominal aorta in the children with bicuspid aortic valve: An observational study. Anadolu Kardiyol Derg 2012;12:413-9.

18. Myung Y, Seo HS, Jung IH, Lee NH, Suh J, Choi JH, et al. The correlation of carotid artery stiffness with heart function in hypertensive patients. J Cardiovasc Ultrasound 2012;20:134-9.

19. Vaes AW, Spruit MA, Theunis J, Goswami N, Vanfleteren LE, Franssen FME, et al. Endothelial function in patients with chronic obstructive pulmonary disease: A systematic review of studies using flow mediated dilatation. Expert Rev Respir Med 2017;11:1021-31.

20. Yanagawa B, Butany J, Verma S. Update on rheumatic heart disease. Curr Opin Cardiol 2016;31:162-8.

21. Hafez M, Yahia S, Eldars W, Eldeгля H, Matter M, Attia G, et al. Prediction of residual valvular lesions in rheumatic heart disease: Role of adhesion molecules. Pediatr Cardiol 2013;34:583-90.

22. Yeğin O, Coşkun M, Ertuğ H. Cytokines in acute rheumatic fever. Eur J Pediatr 1997;156:25-9.

23. Dzikowska-Diduch O, Domienik-Karłowicz J, Górska E, Demkow U, Pruszczyk P, Kostrubiec M. E-selectin and sICAM-1, biomarkers of endothelial function, predict recurrence of venous thromboembolism. Thromb Res 2017;157:173-80.

24. Ramesh G, Varma JS, Ganguly NK, Dhawan V, Bali HK, Singh M. Increased plasma nitrite level in cardiac failure. J Mol Cell Cardiol 1999;31:1495-500.

25. Ci HB, Ou ZJ, Chang FJ, Liu DH, He GW, Xu Z, et al. Endothelial microparticles increase in mitral valve disease and impair mitral valve endothelial function. Am J Physiol Endocrinol Metab 2013;304:E695-702.

26. Horstman LL, Jy W, Jimenez JJ, Ahn YS. Endothelial microparticles as markers of endothelial dysfunction. Front Biosci 2004;9:1118-35.

27. Huang PL. Endothelial nitric oxide synthase and endothelial dysfunction. Curr Hypertens Rep 2003;5:473-80.

28. Çiftel M, Yılmaz O, Kardelen F, Kocabaş A. Carotid intima media thickness and arterial stiffness in children with acute rheumatic fever. Pediatr Cardiol 2014;35:16-21.