Cardiology in the Young

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Cardiac functions and aortic elasticity in children with inflammatory bowel disease: effect of age at disease onset

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Abstract

Aim: Childhood onset inflammatory bowel disease is more aggressive and has rapidly progressive clinical course than adult inflammatory bowel disease. Early-onset inflammatory bowel disease has more severe clinical progression as a subspecialised group of monogenic inflammatory bowel disease. We studied cardiac functions and aortic elasticity in children with early- and late-onset inflammatory bowel disease in remission period. *Methods:* Thirty-three paediatric patients were divided into subgroups according to age of disease onset (<10 and >10 years of age). Twenty-five healthy children were admitted as control group. M-Mode echocardiography and pulsed wave Doppler echocardiography were performed. Strain, distensibility, stiffness index of ascending, and abdominal aorta were evaluated. *Results:* Interventricular septum (mm) and left ventricular end-systolic diameter were higher (6.9 ± 1.2, 26.2 ± 4.6) in early-onset inflammatory bowel disease patients than control patients (6.1 ± 1.27, 22.7 ± 4.12) ($p = 0.050$, $p = 0.050$). Mitral E/E′ ratio and myocardial performance index were increased in inflammatory bowel disease and early-onset inflammatory bowel disease groups than control group ($p = 0.046$, $p = 0.04$; $p = 0.023$, $p = 0.033$). Diastolic functions were found to be impaired in inflammatory bowel disease and early-onset inflammatory bowel disease groups according to control group, while there was no difference between late-onset inflammatory bowel disease and control groups in terms of diastolic functions. Mitral E/A ratio was lower in inflammatory bowel disease patients and early-onset inflammatory bowel disease patients (1.46 ± 0.32, 1.4 ± 0.21) than control patients (1.70 ± 0.27) ($p = 0.013$, $p = 0.004$). Aortic elasticity did not differ between groups. *Conclusion:* Chronic low-grade inflammation has effects on left ventricular diameters and diastolic function in remission period. Aortic elasticity is not affected in our study groups.

Inflammatory bowel disease (Crohn's disease, ulcerative colitis) is characterised by chronic inflammation of the intestine. Inflammation of gut causes increased intestinal permeability, which triggers immune response to the luminal antigens.[1,2] Therefore, inflammatory bowel disease is a systemic disorder that is not restricted to the intestinal tract solely. Extraintestinal involvement is seen in 20–40% inflammatory bowel disease patients.[3,4]

Myocardial, pericardial, valvular, and vascular involvement can be seen in inflammatory bowel disease.[5,6] Venous thromboembolism and ischemic heart disease are the other problems.[7,8]

Besides acute inflammatory exacerbations of inflammatory bowel disease, there is an ongoing chronic inflammation in remission periods. Classical cardiovascular risk factors such as obesity, diabetes, dyslipidemia, and hypertension are lower in inflammatory bowel disease patients than normal population.[9,10] This gives an opportunity to evaluate the effects of chronic inflammation on myocardial function and elasticity of the great vessels in inflammatory bowel disease ideally. Subclinical myocardial systolic and diastolic dysfunctions were shown by strain echocardiography in both paediatric and adult inflammatory bowel disease patients.[11] Elasticity of aorta was shown to be related to the disease activity in adult inflammatory bowel disease patients.[12] Also, there is no study investigating aortic elasticity in remission periods either in adults or in children.

It is known that age at diagnosis in inflammatory bowel disease has a prognostic effect on disease progression. Diagnosis of inflammatory bowel disease before 10 years of age causes differences in disease location and treatment.[13] These differences were related to genetic factors. Myocardial involvement or aortic elasticity properties are not known in this patient group. We subgrouped inflammatory bowel disease patients according to disease onset and studied left ventricular dimensions, systolic and diastolic functions, and aortic elasticity.

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Method

Patients

Patients in remission period followed with diagnosis of inflammatory bowel disease in paediatric gastroenterology clinic were admitted to the study. Patients were in remission period for at least 1 year. There were 33 inflammatory bowel disease patients (17 male/16 female; 5–18 years of age, mean age 13.3 ± 3.9; 15 Chron's disease and 18 ulcerative colitis) in study group and 25 patients (13 male/12 female; 6–18 years of age, mean age 11.6 ± 4) in control group. Patients were divided into subgroups according to age at diagnosis (early-onset inflammatory bowel disease was defined as the patients diagnosed under 10 years of age and late-onset inflammatory bowel disease was defined as the patients diagnosed over 10 years of age). There were 14 early-onset inflammatory bowel disease patients (mean age 9.5 ± 2.9) and 19 late-onset inflammatory bowel disease patients (mean age 16.1 ± 1.25) in study group. Comparison between these groups was not susceptible as mean ages of early and late onset were not similar to each other. Left ventricular dimensions and Doppler measurements are age-dependent, so statistical evaluation was performed within early-onset inflammatory bowel disease versus control group and late-onset inflammatory bowel disease versus control group. Inflammatory bowel disease was diagnosed by using clinical symptoms, radiological, endoscopic, and histopathological findings. The duration of disease, disease activity index according to paediatric ulcerative colitis activity index, and paediatric Crohn's disease activity index were obtained from patients' medical recordings.[14,15] All patients had no other systemic or cardiac disease. Blood pressure of all patients was measured by sphygmomanometry before echocardiographic evaluation. Serum glucose level and lipid profile were examined. None of them had diagnosis of diabetes mellitus, hypertension, and hyperlipidemia.

Control patients were healthy children who referred to paediatric cardiology clinic with innocent murmur. Patients gave written consents for the study and the study was approved by the local ethics committee in Istanbul University of Health Sciences, Umraniye Education and Research Hospital on 25 June, 2018.

Echocardiography

Echocardiographic evaluation was performed in all subjects using Philips Affiniti 50C (22100 Bothell – Everett Highway Bothell, VVA 98021-8431) echocardiography machine and 8–4 MHz transducer. Left ventricular systolic and diastolic diameters (LVSd, LVDd), diameter of interventricular septum (IVSd), and left ventricular posterior wall (LVPWd) were measured by M-Mode echocardiography in parasternal long-axis view, and ejection fraction (EF) and shortening fraction (SF) were calculated from M-Mode measurements. Mitral inflow parameters, mitral E velocity, mitral A velocity, deceleration time (DT), and interventricular contraction time (IVRT) were evaluated by pulsed wave Doppler echocardiography. Mitral E′ wave, mitral A′ wave, isovolumetric contraction time (IVCT), isovolumetric relaxation time (IVRT), and ejection time (ET) were measured by tissue Doppler echocaridography. Myocardial performance index was calculated according to formula IVCT + IVRT/ET. Systolic and diastolic diameters of ascending aorta and abdominal aorta were measured, and strain, distensibility (DIS), and stiffness index (SI) were calculated according to below formulas:

$$\text{Aortic strain}\,(\%) = 100 \times (\text{Systolic diameter} - \text{Diastolic diameter}) / \text{Diastolic diameter}$$

$$\text{Aortic stiffness index} = \text{logarithm}\,(\text{Systolic blood pressure}/\text{Diastolic blood pressure}) / ((\text{Systolic diameter} - \text{Diastolic diameter})/\text{Diastolic diameter})$$

$$\text{Aortic distensibility}\,(\text{cm}^2/\text{dyn}^2/10^{-6}) = 2 \times (\text{Systolic diameter} - \text{Diastolic diameter}) / (\text{Diastolic aortic diameter}) \times (\text{Systolic blood pressure} - \text{Diastolic blood pressure})$$

Statistical analysis

The data were analysed using SPSS 22 software package (IBM Corp., Armonk, New York, United States of America). The distribution of normality was analysed using Kolmogorov–Simirnov test. Data were expressed as mean ± standard deviation or median and range for continuous variables; for categorical variables, number and percentages (%) were expressed. Comparison of groups' inflammatory bowel disease versus control and early-onset inflammatory bowel disease versus control and late-onset inflammatory bowel disease versus control was made by using Student t-test and Mann–Whitney U-test whichever is appropriate. Spearman rank correlation coefficient was used for analysis of correlations between variables. Statistical significance was considered a $p < 0.05$.

Results

Patients

The mean duration of illness was 29.4 ± 23.4 months (3–96 months, median time = 2 months; 1–84 months, median time = 23 months). Activity index of patients at diagnosis was 51.3 ± 12.8 (35–85, median = 50) and activity index during the clinical evaluation of the study was 7.1 ± 8.4 (0–30, median = 5). The average age of the study group was 13.3 ± 3.9, the mean age was 9.5 ± 2.97 in early-onset inflammatory bowel disease, 16 ± 1.2 in late-onset inflammatory bowel disease, and 11.6 ± 4 in control group. There was statistically significant difference between early-onset inflammatory bowel disease and late-onset inflammatory bowel disease groups in terms of age ($p = 0.04$). However, there was no statistical significance in comparison of age in groups' between early-onset inflammatory bowel disease versus control and late-onset inflammatory bowel disease versus control. One patient had perianal involvement and four patients had extraintestinal involvement. Nine of the patients were under Mesalamine treatment and 18 of them were treated with Mesalamine and Azathiopurine, 3 patients were taking Infliximab in addition to Mesalamine, and 3 patients were taking Infliximab, Mesalamine, and Azathiopurine therapy. Demographic and clinical data were shown in Table 1.

Echocardiography

M-mode echocardiography and mitral inflow parameters

In early-onset inflammatory bowel disease patients, interventricular septum (mm) was thicker (6.9 ± 1.2) than control patients (6.1 ± 1.27) ($p = 0.050$). Left ventricular end-systolic diameter (mm) was higher in early-onset inflammatory bowel disease patients

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Table 1. Demographic and clinical data of IBD and control patients

	IBD	Control	p
Demoghraphic features			
Gender (male/female)	17/16 (33)	13/12 (25)	0.50
Age (years)	13.3 ± 3.9	11.6 ± 4	0.33
Weight (kg)	45.5 ± 20.7	40.7 ± 16.6	0.56
Height (cm)	147 ± 24	147.7 ± 21	0.95
BMI	19.1 ± 4.09	17.7 ± 2.8	0.21
SBP (mmHg)	106 ± 11.6	102.9 ± 10.9	0.13
DBP (mmHg)	65.5 ± 9	60.5 ± 10.2	0.71
PP (mmHg)	40.4 ± 11.2	42.3 ± 6.4	0.21
M-mode echocardiography			
IVSd/m^2	6.1 ± 1.28	6.1 ± 1.27	0.963
LVSd/m^2	23.8 ± 4.07	22.7 ± 4.12	0.677
LVDd/m^2	35.9 ± 6.2	36.5 ± 8.3	0.926
LVPWd/m^2	4.34 ± 0.66	4.47 ± 0.82	0.516
EF (%)	63.2 ± 4.27	67.4 ± 5.7	0.061
SF (%)	34.2 ± 3.76	37.7 ± 5.3	0.119
Pulsed wave and tissue Doppler echocardiography			
Mitral E (cm/s)	93.6 ± 16.9	97.3 ± 15.4	0.160
Mitral A (cm/s)	65.7 ± 14.7	59.1 ± 13.4	0.190
DT (s)	151.1 ± 26.4	127 ± 44.7	0.045
IVRT (s)	65 ± 16.9	60.6 ± 6.45	0.353
E/A	1.46 ± 0.32	1.70 ± 0.27	0.013
Mitral E′	17.8 ± 3.47	18 ± 3.21	0.55
Mitral A′	8.1 ± 1.19	7.9 ± 0.87	0.40
Mitral E/E′	0.051 ± 0.02	0.045 ± 0.037	0.046
IVCT	64.1 ± 18	66 ± 6.8	0.09
IVRT	62 ± 17	60 ± 12	0.88
ET	255 ± 60	253 ± 40	0.99
MPI	68 ± 11	62 ± 13	0.04
Elasticity parameters of ascending aorta			
Strain (%)	8.35 ± 4.9	9.29 ± 4.65	0.127
DIS (cm^2/dyn/10^6)	7.70 ± 3.63	8.08 ± 2.79	0.728
SI	6.01 ± 2.5	7.4 ± 3.35	0.502
Elasticity parameters of abdominal aorta			
Strain (%)	9.58 ± 3	8.85 ± 2.78	0.530
DIS (cm^2/dyn/10^6)	7.61 ± 2.16	7.65 ± 2.17	0.662
SI	4.37 ± 2.31	6.7 ± 2.8	0.095

BMI = body mass index; DBP = diastolic blood pressure; DT = desceleration time; ET = ejection time; IBD = inflammatory bowel disease; IVCT = isovolumetric contraction time; IVRT = isovolumetric relaxation time; IVSd = interventricular septal diameter; LVDd = left ventricular diastolic diameter; LVPWd = left ventricular posterior wall diameter; LVSd = left ventricular systolic diameter; m^2 = body surface area; Mitral A = mitral peak late wave velocity; Mitral A′ = tissue Doppler imaging septal annular velocity during atrial contraction; Mitral E = mitral peak early wave velocity; Mitral E′ = tissue Doppler imaging mitral early diastolic septal annular velocity; MPI = myocardial performance index; PP = pulse pressure; SBP = systolic blood pressure; SI = stiffness index.

(26.2 ± 4.6) than control patients (22.7 ± 4.12) (p = 0.050) (Table 2).

Mitral E/A ratio was lower in inflammatory bowel disease patients (1.46 ± 0.32) than control patients (1.70 ± 0.27) (p = 0.013). DT (seconds) was longer in inflammatory bowel disease patients (151.1 ± 26.4 seconds) than control patients (127 ± 44.7 seconds) (p = 0.045).

Mitral A was higher in early-onset inflammatory bowel disease patients (68.3 ± 10.6) than control patients (59.1 ± 13.4) (p = 0.012). Mitral E/A ratio was lower in early-onset inflammatory bowel disease patients (1.4 ± 0.21) than control patients (1.70 ± 0.27) (p = 0.004). DT (seconds) was longer in early-onset inflammatory bowel disease patients (149.2 ± 28.3) than control patients (127 ± 44.7) (p = 0.012). Tissue Doppler echocardiography revealed increment of E/E′ ratio and myocardial performance index in inflammatory bowel disease and early-onset inflammatory bowel disease groups according to control group (p = 0.046, p = 0.04; p = 0.023, p = 0.033). E′ was decreased in early-onset inflammatory bowel disease than control group (p = 0.05) (Table 2).

Elasticity parameters

There was no statistically significant difference in aortic elasticity parameters of ascending and abdominal aorta between inflammatory bowel disease and control patients. Elasticity parameters did not differ between early-onset and control patients and between late-onset and control patients (Table 2).

Discussion

Inflammatory bowel disease is a chronic inflammatory disease with exacerbation and remission periods. During acute exacerbations, endocardial, myocardial, and pericardial involvement are expected.[7,16] In remission periods, inflammation continues at low grade.

It is well known that inflammation causes endothelial dysfunction and has effects on structure and function of arterial wall.[17,18] Endothelial dysfunction exists not only in the endothelium of gut in inflammatory bowel disease, it has arterial extent. Chronic systemic low-grade inflammation affects both endothelial function and elastic properties of the great vessels. Inflammatory mediators causes increased matrix metalloproteinase activity and elastin degradation in the arterial wall inducing impaired arterial stiffness.[19] Arterial stiffness is a marker of the end organ damage of systemic inflammation and accepted as a predictor of cardiovascular mortality and morbidity.[20] Increased arterial stiffness was found in adult inflammatory bowel disease patients.[21,22] Meta-analysis found a link between inflammation and aortic stiffness in inflammatory bowel disease patients and it was related to the duration of the disease.[21] There is only one study evaluating the arterial stiffness in children which did not found a statistical difference between inflammatory bowel disease and control patients. In that study the remission rate of patients was 68%.[23] In our study, all of the patients were in remission and there was no statistically significant difference in the elasticity of ascending and abdominal aorta between groups and subgroups. As arterial stiffening is an early marker of cardiovascular risk, it should be followed up in young adulthood. Our study showed that arterial stiffening was not increased in children while they were in remission.

Endocardial endothelium which is a biologic barrier between blood and myocytes has effects on myocyte contractility and

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Table 2. Echocardiographic features and aortic elasticity parameters of early-onset and late-onset inflammatory bowel disease and control patients

	Early-onset IBD	Late-onset IBD	Control	p*	p**
M-Mode echocardiography					
IVSd/m^2 (mm)	6.9 ± 1.2	5.1 ± 0.6	6.1 ± 1.27	0.050	0.054
LVDd/m^2 (mm)	43.9 ± 7.2	31 ± 3.6	36.5 ± 8.3	0.075	0.065
LVDs/m^2 (mm)	26.2 ± 4.6	19.9 ± 3.9	22.7 ± 4.12	0.050	0.26
LVPWd/m^2 (mm)	4.7 ± 0.6	3.8 ± 0.5	4.47 ± 0.82	0.27	0.063
SF (%)	35 ± 3.3	34.8 ± 4.4	37.7 ± 5.3	0.19	0.23
EF (%)	64.7 ± 4.5	63.2 ± 4.3	67.4 ± 5.7	0.19	0.11
Pulsed wave and tissue Doppler echocardiography					
MitralE (cm/s)	96.8 ± 9.2	86.7 ± 20	97.3 ± 15.4	0.98	0.076
Mitral A (cm/s)	68.3 ± 10.6	61 ± 8.3	59.1 ± 13.4	0.012	0.070
E/A	1.4 ± 0.21	1.5 ± 0.4	1.70 ± 0.27	0.004	0.064
DT (s)	149.2 ± 28.3	152 ± 47.9	127 ± 44.7	0.012	0.28
IVRT (s)	59.3 ± 10.6	68.8 ± 18.9	60.6 ± 6.45	0.98	0.20
Mitral E′	17 ± 2.78	18.1 ± 3.1	18 ± 3.21	0.05	0.65
Mitral A′	8 ± 1.19	8.1 ± 1.23	7.9 ± 0.87	0.44	0.42
Mitral E/E′	0.052 ± 0.01	0. 05 ± 0.04	0.045 ± 0.037	0.023	0.23
IVCT	61.1 ± 10.2	65 ± 28	66 ± 6.8	0.082	0.08
IVRT	61.8 ± 19.1	63 ± 19	60 ± 12	0.93	0.89
ET	267 ± 50	250 ± 70	253 ± 40	0.99	0.79
MPI	66 ± 10.2	64 ± 19	62 ± 13	0.033	0.18
Elasticity parameters of ascending aorta					
Strain (%)	9.3 ± 6	8.6 ± 3.1	9.29 ± 4.65	0.062	0.459
DIS (cm^2/dyn/10^6)	8.6 ± 4.2	6.7 ± 2.7	8.08 ± 2.79	0.41	0.525
SI	6.3 ± 3	5.4 ± 2.2	7.4 ± 3.35	0.89	0.651
Elasticity parameters of abdominal aorta					
Strain (%)	10.3 ± 2.8	9 ± 3.4	8.85 ± 2.78	0.17	0.756
DIS (cm^2/dyn/10^6)	8.3 ± 1.5	6.6 ± 2.5	7.65 ± 2.17	0.06	0.481
SI	5.8 ± 2.3	3.96 ± 2.32	6.7 ± 2.8	0.87	0.143

DIS = distensibilite; DT = desceleration time; ET = ejection time; IBD = inflammatory bowel disease; IVCT = isovolumetric contraction time; IVRT = isovolumetric relaxation time; IVSd = interventricular septal diameter; LVDd = left ventricular diastolic diameter; LVPWd = left ventricular posterior wall diameter; LVSd = left ventricular systolic diameter; Mitral A = mitral peak late wave velocity; Mitral A′ = tissue Doppler imaging septal annular velocity during atrial contraction; Mitral E = mitral peak early wave velocity; Mitral E′ = tissue Doppler imaging mitral early diastolic septal annular velocity; MPI = myocardial performance index; SI = stiffness index.
*p: early-onset IBD versus control.
**p: late-onset IBD versus control.

remodelling via endocrine signalling.[24,25] Endocardial endothelial function was found to be impaired in inflammation.[26–28] Endocardial endothelial dysfunction may explain the subclinical diastolic dysfunction in inflammatory bowel disease. In our study, decreased E/A ratio and prolonged DT in inflammatory bowel disease patients indicate impaired diastolic function. Tissue Doppler echocardiography revealed impaired myocardial performance index and E/E′ in inflammatory bowel disease and early onset-inflammatory bowel disease patients according to control patients. In previous studies, diastolic dysfunction was shown in both paediatric and adult inflammatory bowel disease patients.[11,29] Also, diastolic dysfunction was found to be correlated to coronary microvascular dysfunction in adult patients with no coronary risk factors in inflammatory bowel disease patients.[30]

Early-onset inflammatory bowel disease defined as a monogenic inflammatory bowel disease group which is characterised with hyperinflammation and accompanied by autoinflammatory disorders. Monogenic disorders are more resistant to conventional therapy and have a high morbidity and mortality. Early-onset inflammatory bowel disease patients had impaired myocardial diastolic function when compared with control patients, while there

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was no difference between late-onset inflammatory bowel disease patients and control patients in our study.

Left ventricular EF was found to be depressed; left atrial enlargement and increased interventricular septum thickness were revealed in adult inflammatory bowel disease patients in previous studies.[31,32] Left ventricular end-systolic dimension has a prognostic importance on reverse remodelling in patients diagnosed with heart failure.[33] Left ventricular myocardial performance parameters were found to be depressed by speckle tracking echocardiography in inflammatory bowel disease.[11,29] In our study, we determined increase in septal and left ventricular end-systolic diameter in patients with early-onset inflammatory bowel disease. We can conclude that precaution in cardiac evaluation is necessary in early-onset inflammatory bowel disease subgroup.

Limitations

However, this study consisted of small participants' number; it gives information of both aortic elasticity and cardiac function in early- and late-onset inflammatory bowel disease patients in remission period. Although pulse wave velocity is the recommended method for determination of aortic elasticity properties in both children and adults, transthoracic echocardiographic evaluation of aortic elasticity is feasible.[33,29]

Conclusion

We demonstrated diastolic dysfunction and enlargement of systolic left ventricular dimension in early-onset inflammatory bowel disease patients in remission period. Aortic elasticity was not impaired in remission in our study. Long-term follow-up of aortic elasticity parameters in inflammatory bowel disease patients and attention to cardiac involvement in early-onset inflammatory bowel disease subgroup are needed.

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Conflict of Interest. None.

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