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Original Article

The association of epicardial fat thickness and disease severity among Fabry patients

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Abstract

Aim: Patients with Fabry disease frequently die due to cardiovascular causes. There are numerous findings of cardiovascular involvement in patients with Fabry disease. Epicardial fat thickness is a surrogate for various cardiovascular diseases. In this study, we evaluated epicardial fat thickness and parameters of diastolic dysfunction among Fabry patients as a possible indicator of disease severity.

Materials and Methods: We enrolled 14 patients with Fabry disease who receive enzyme replacement therapy. Detailed echocardiographic examination was performed including diastolic functions and measurement of epicardial fat thickness. Disease severity was assessed using DS3 scoring system. Based on DS3 scores, patients are grouped into mild (<10 points), moderate (10-28 points) and severe (29-32 points) disease.

Results: There were two female and twelve male patients with Fabry disease. Patients were classified into three groups based on DS3 scores. Epicardial fat thickness was significantly increased among patients with advanced disease compared to patients with mild disease (p:0.002). Also, epicardial fat thickness had significant positive correlation with average E/E' ratio (p:0.014), left atrial volume (p:0.004) and left atrial volume index (p:0.022).

Conclusion: Epicardial fat thickness seems as a promising new marker of disease severity among patients with Fabry disease.

Keywords: Fabry's disease; inflammation; echocardiography.

INTRODUCTION

Fabry disease is a rare X linked disease which affects nearly 1 in 100.000 live births. The problem is deficient a-galactosidase enzyme which results accumulation of globotriaosylceramide within lysosomes. Affected individuals generally remain asymptomatic until adulthood. The most frequent early signs are painful extremities (neuropathy) and skin lesions (angiokeratomas) (1). Renal dysfunction is common but cardiovascular system involvement is the most common cause of death in both genders among Fabry patients (2).

Epicardial adipose tissue (EAT) is located between myocardium and visceral pericardium. Due to this anatomic location, epicardial adipose tissue has important roles on the functions of the heart. In addition to the local effects, epicardial adipose tissue is nourished by coronary arteries and thus this tissue exerts systemic effects by secreting adipokines, proinflammatory and anti-inflammatory cytokines. Currently, epicardial fat thickness is associated with many disease states, especially coronary atherosclerosis, insulin resistance, heart failure, atrial fibrillation, metabolic syndrome and fatty liver disease (3).

A wide range of acute and chronic inflammatory processes are activated in patients with Fabry disease and currently it is believed that inflammatory response also plays an important role in the pathogenesis and progression of the disease (4).

Since the majority of Fabry patients die due to cardiovascular causes, follow-up of Fabry patients at cardiology clinics is of paramount importance. The main findings of cardiac involvement are echocardiographically documented concentric left ventricle hypertrophy, replacement fibrosis, reduced tissue Doppler velocities, right ventricular hypertrophy, and arrhythmias (1). In this study, we sought to evaluate the association of echocardiographic epicardial fat thickness and disease severity among patients with Fabry disease.

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MATERIALS and METHODS

Between May and September 2017, 14 patients with Fabry disease were enrolled to the study. Approval of the local ethics committee and patient informed consents were obtained before the enrollment (Ethics committee accepting number: 2017/274). Weight and height of all patients were recorded, body-mass index and body surface area of all patients were calculated and recorded.

All patients underwent detailed echocardiographic examination. Epicardial fat thickness (EFT)is measured from parasternal long-axis view, as the echo-free space between the outer wall of the myocardium and the visceral pericardium. Measurement was performed perpendicular to the aortic annulus as a landmark for three cardiac cycles (5). Diastolic flow volumes (E and A waves) were recorded at mitral leaflet tips during diastole at apical four-chamber view. Tissue Doppler parameters were obtained from apical 4-chamber view from septal and lateral walls and all parameters of diastolic functions were recorded according to the recommendations of the American Society of Echocardiography (6). Left atrial volumes were calculated using the area-length approximation method (7). We measured leukocyte alphagalactosidase A activity as the initial diagnostic test and then we confirmed the Fabry disease diagnosis with mutation analysis. The severity of Fabry disease was calculated according to current Fabry disease severity scoring system (DS3). DS3 system consisted of peripheral nervous system clinical findings (sweating, gastrointestinal and pain), renal system evaluation (eGFR with MDRD equation and proteinuria evaluation), cardiac evaluation (left ventricle hypertrophy, arrhythmia presence and NYHA class), central nervous system work up (white matter lesions presence and history of TIA/stroke) and patients reported well-being state (8,9). According to this system, we grouped patients into three disease severity levels; mild (<10 points), moderate (10-28 points) and severe (29-32 points). Statistical analysis was performed using SPSS 18.0 (SPSS, Chicago, IL).

Statistical Analysis

Approval of the Medical Ethics Committee was obtained and informed consent was signed by each patient. Data were expressed as number, percentage, and mean ± standard deviation. Correlations between numerical variables were tested using correlation analysis. Correlations between parameters were evaluated with Pearson and Spearman correlation tests. Two-sided values of $p < 0.05$ were considered as statistically significant. Statistical analysis was performed using SPSS 18.0 statistical software.

RESULTS

Fourteen patients with enzymatically and genetically diagnosed Fabry disease were enrolled to the study. There were only two females and all other patients were male. Mean age was 35.71 years. Demographic data and variables are summarized in Table 1 and Table 2. We used DS3 scoring system for grading Fabry disease severity and according to this system, we grouped patients into three status; mild disease (<10 points), moderate disease (10-28 points) and severe disease (29-32 points). There were 5 patients with mild disease, 6 patients with moderate disease and 3 patients with severe disease. Epicardial

Table 1. Descriptive statistics of the patients

	Minimum	Maximum	Mean	Std Deviation
Age (years)	23	52	35.71	9.6
BMI (kg/m^2)	16.51	29.78	22.21	3.47
BSA (m^2)	1.18	2	1.56	0.24
eGFR (mL/min/1.73m^2)	62.4	188.3	120.33	39.87
DS3 Score	9	32	17.85	9.55
EFT (mm)	5.53	10.52	7.61	1.5
E/E' (Average)	5.82	11.8	8.35	1.9
LAV (mL)	27.76	103.26	47.33	19.15
LAVI (mL/m^2)	20.41	67.05	29.96	12.03

BMI: Body mass index, BSA: Body surface area, eGFR: estimated glomerular filtration rate (based on MDRD formula), EFT: Epicardial fat thickness, LAV: Left atrial volume, LAVI: Left atrial volume index, E/E': echocardiographic parameter of left ventricular diastolic function (mitral valve diastolic inflow velocity/tissue Doppler diastolic annular velocity).

Table 2. Age, BMI and laboratory values of the patients according to the DS3 scores

DS3 Score	Age (years)	BMI (kg/m^2)	CRP (mg/dL)	Proteinuria (mg/24h)
Mild (<10 points)	29.6 ± 5.68	22.05±3.84	3.4 ±3.54	248.4 ±35.5
Moderate (11-28 points)	39.66±11	22.24±4.08	2.47 ±3.56	478.4 ±75.5
Severe (29-32 points)	38±9.16	22.40±2.63	2.54 ±1.43	848.4 ±105.5

BMI: Body mass index, CRP: C-reactive protein

fat thickness (EFT) was significantly increased among patients with higher DS3 scores (p:0.002). In addition, EFT also showed significant correlation with parameters of diastolic dysfunction. There were significant positive correlations between EFT and average E/E' (p:0.014), EFT and left atrial volume (p:0.004) and EFT and left atrial volume index values (p:0.022). Results of correlation analysis are summarized in Table 3.

Table 3. Results of the correlation analysis

	DS3 Score	E/E' Average	LAV	LAVI
EFT	0.002			
Pearson correlation	(R1: 0.86 R2: 0.75)	0.014	0.004	0.022

Correlation is significant at the 0.05 level. EFT: Epicardial fat thickness, LAV: Left atrial volume, LAVI: Left atrial volume index, E/E': echocardiographic parameter of left ventricular diastolic function (mitral valve diastolic inflow velocity/tissue Doppler diastolic annular velocity).

DISCUSSION

Our study shows, for the first time that, epicardial fat thickness is significantly increased among patients with advanced Fabry disease compared to Fabry patients with mild disease.

Epicardial fat thickness is being extensively investigated in a multitude of diseases. Iacobellis et al were among first investigators to describe the clinical correlation of epicardial fat thickness. They first described that epicardial fat thickness was strongly correlated with visceral adiposity (10). After these findings, a multitude of study has been performed showing various associations of epicardial fat thickness.

The most robust association is increased risk of metabolic syndrome with higher epicardial fat thickness (EFT) measurements. Iacobelliset al (11) revealed that the threshold EFT level for metabolic syndrome was 7.5 mm for women and 9.5 mm for men for the prediction of metabolic syndrome. In our study, mean EFT was 7,48±1.49 mm (min: 5,53 mm max:10.52 mm). There are numerous associations of EFT with systemic disorders. Concistre et al (12) compared EFT values among patients with essential hypertension and patients with autosomal polycystic kidney disease (ADPKD) and they found that EFT was higher in APKD patients and independently correlated with left ventricular mass index. This finding suggests that EFT measurement can be an easy and reproducible way of predicting cardiovascular risk among patients with ADPKD. In another study, Iacobellis et al (13) evaluated EFT in obese patients with evidence of nonalcoholic fatty liver disease. Results showed that EFT had a strong correlation with liver steatosis in obese subjects. EFT may also signify increased risk of systemic thromboembolism. Gürdal et al (14) evaluated EFT among young patients with embolic stroke of unknown origin. They found that patients with embolic stroke of undetermined source had significantly higher EFT measurements compared to healthy controls.

As regards to cardiovascular diseases, the most important clinical correlation is between EFT and coronary artery disease, acute myocardial infarction, malignant arrhythmias and sudden death. Ahn et al (15) showed that epicardial adipose tissue was thicker in patients with coronary artery disease compared to healthy controls. In addition, epicardial adipose tissue was also thicker in patients with unstable angina compared to patients with stable angina and atypical chest pain. Also, Eroglu et al (16) revealed that epicardial adipose tissue thickness had increased with the severity of coronary artery disease and had good correlation with Gensini score. More recently, Park et al (17) studied echocardiographically measured epicardial fat thickness in patients presenting with acute ST elevation myocardial infarction (STEMI). They chose a reference thickness of 3.5 mm for epicardial fat and divided patients into two groups; thick EAT (≥3.5 mm) and thin EAT (<3.5 mm). After a mean follow-up period of 46±18 months, MACE-free survival rate was significantly lower in the thick EAT group compared to thin EAT group. Target-vessel-revascularization (TVR)-free survival was also significantly lower in the thick EAT group. This study shows that epicardial fat thickness has also long-term prognostic implications in patients with acute myocardial infarction.

The most common cause of death among Fabry patients is cardiovascular diseases. In a nation-wide registry performed in the United States, 40% of males and 41.7% of females with Fabry disease had died due to cardiovascular causes (18). Patel et al (19) showed that heart failure was the most common first cardiovascular event among patients with Fabry disease. The most common structural change is concentric hypertrophy. Less frequently, right ventricular hypertrophy and aortic root dilatation is observed. Symptoms are frequently palpitations, dyspnea and angina.

We also found that epicardial fat thickness is significantly associated with diastolic dysfunction among Fabry patients. The most relevant parameters of diastolic dysfunction, mitral valve early diastolic flow rate to tissue Doppler early diastolic velocity ratios (E/E'), left atrial volume and left atrial volume index had significant positive correlation with EFT (p: 0.014, p:0.004 and p:0.022 respectively). The association of EFT with diastolic dysfunction was studied and demonstrated in multiple studies. Dabbah et al (20) evaluated diastolic functions and measured epicardial fat among 73 healthy volunteers and found that epicardial fat thickness was significantly associated with diastolic dysfunction. Also, Hachiya et al (21) revealed that epicardial fat thickness had a positive correlation with increasing severity of diastolic dysfunction among patients with coronary artery disease. In our study, we also observed that average E/E' ratio significantly correlated with increasing epicardial fat thickness (p:0.014). As one of the most sensitive and specific indicators of chronic diastolic

dysfunction, left atrial volume and left atrial volume index had also significant positive correlation with epicardial fat thickness (p:0.004 and p:0.022 respectively). Our findings suggest that, like in healthy population, epicardial fat thickness is a marker of diastolic dysfunction among patients with Fabry disease.

Our major limitation is that we performed a single center study. Despite the fact that we have highest number of Fabry patients in any institution in our country, multicenter studies give more generalizable results. Cardiac MRI and cardiac CT are also used for quantifying epicardial fat thickness. Correlation with these techniques would strengthen our findings. Besides our study had cross sectional design it would be more fruitful if the follow up data of the disease progression exist.

In conclusion, our findings suggest epicardial fat thickness as a new index of disease severity among patients with Fabry disease.

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