Assessment of aortic stiffness and ventricular functions in familial Mediterranean fever

Ailevi Akdeniz ateşinde aortik sertleşme parametrelerinin ve ventrikül fonksiyonlarının değerlendirilmesi

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ABSTRACT

Objective: To investigate systolic and diastolic ventricular functions, aortic elastic properties and the presence of pericardial effusion in familial Mediterranean fever (FMF) patients.

Methods: A case-controlled, cross-sectional study was performed on 44 FMF patients and 27 controls. Subjects with hypertension, diabetes mellitus and hyperlipidemia were excluded. Left and right ventricular functions were measured using echocardiography including two-dimensional, M-mode, and conventional Doppler as well as pulsed wave tissue Doppler imaging (TDI). Aortic elasticity was analyzed using M-mode tracing guided by the two-dimensional echocardiography. Statistical analysis was performed using Mann Whitney U, Spearman rho correlation and Fisher's exact tests.

Results: Age, sex, body mass index, smoking status and lipids were comparable in patients and controls ($p>0.05$). None of the subjects had pericarditis and/or pericardial effusion. Aortic wall properties were similar between groups ($p>0.05$). The TDI parameters of mitral lateral annulus revealed significantly lower Em/Am ratios in patients compared to controls [1.77 (0.6-3.4) vs. 1.79 (0.9-4.8), $p=0.02$]. Mitral flow propagation velocity was significantly lower in patients than healthy subjects [63 (39-100) vs. 74 (40-94) cm/s, $p=0.008$]. Tricuspid annular plane systolic excursion (TAPSE) was significantly reduced in FMF group than in controls [2 (1.3-2.5) vs. 2.5 (1.7-3.2) cm; $p<0.001$]. Eight of the patients and one control had impaired TAPSE (<2 cm; $p=0.025$). There was no difference regarding right ventricular diastolic dysfunction (RVDD) as assessed by using standard Doppler echocardiography ($p>0.05$). However, pronounced RVDD was observed in FMF patients documented by TDI (Em/Am<1; 19 patients vs. 0 controls, $p<0.001$).

Conclusion: Subclinical myocardial involvement is present in a cohort of relatively young FMF patients who were also free of classical cardiovascular risk factors. Pericardium and aorta seem to be spared during attack free periods of FMF. *(Anadolu Kardiyol Derg 2008; 8: 271-8)*

Key words: Aortic stiffness, cardiac disease, Doppler echocardiography, familial Mediterranean fever, ventricular dysfunction

ÖZET

Amaç: Bu çalışmada Ailevi Akdeniz Ateşi (AAA) hastalarında aortun elastik özelliklerinin, ventrikül fonksiyonlarının ve perikardiyal efüzyon varlığının değerlendirilmesini amaçladık.

Yöntemler: Bu vaka-kontrollü, enine-kesitsel çalışmada 44 AAA hastası ve 27 sağlıklı birey yer aldı. Hipertansiyon, diyabet ve dislipidemisi olan bireyler çalışmaya alınmadı. Sağ ve sol ventrikül fonksiyonlarının değerlendirilmesinde 2-boyutlu, M-mod, standart ve doku Doppler ekokardiyografi incelemeleri kullanıldı. Aortun elastik özelliklerinin incelenmesinde 2-boyutlu ve M-mod ekokardiyografi kullanıldı. İstatistiksel değerlendirmede Mann Whitney U, Fisher testi ve Spearman korelasyonu kullanıldı.

Bulgular: Hasta ve kontrol grubu yaş, cins, sigara kullanma durumu, vücut kitle indeksi- ve serum lipid düzeyleri açısından benzer özellikteydi ($p>0.05$). Çalışma grubundaki hiçbir bireyde perikardit ve/veya perikardiyal efüzyonla ilişkin bulguya rastlanmadı. Aortik elastik fonksiyon parametreleri hasta ve kontrol gurupları arasında benzerdi ($p>0.05$). Doku Doppler ile elde edilen sol ventrikül mitral annuler Em/Am oranı hasta grubunda kontrollere göre anlamlı olarak düşüktü [1.77 (0.6-3.4) karşı 1.79 (0.9-4.8) $p=0.02$]. Öte yandan mitral renkli M-mod akım yayılma hızı (Vp) hasta grubunda anlamlı olarak kısa bulundu [63 (39-100) karşı 74 (40-94) cm/s, $p=0.008$]. Triküspid annuler düzlem sistolik hareketi (TAPSE) değeri AAA hastalarında kontrollere göre belirgin düşüktü [2 (1.3-2.5) vs. 2.5 (1.7-3.2) cm; $p<0.001$]. Sekiz AAA hastası ve bir kontrolde TAPSE değeri <2 cm bulundu ($p=0.025$). Standart Doppler değerlendirmesi ile sağ ventrikül fonksiyonlarında hasta ve kontrol grubu arasında fark izlenmezken doku Doppler ile elde edilen değerlendirmede AAA hastalarında artmış sağ ventrikül diyastolik disfonksiyonu vardı (Em/Am<1; 19 AAA vs. 0 kontrol, $p<0.001$).

Sonuç: Bu çalışmadaki bulgular klasik kardiyovasküler risk faktörü olmayan ve nispeten genç yaştaki AAA hastalarında subklinik bir miyokardiyal tutulumu düşündürtmektedir. Öte yandan aort ve perikardiyumun bu hastalarda etkilenmediği gözlenmiştir. *(Anadolu Kardiyol Derg 2008; 8: 271-8)*

Anahtar kelimeler: Aortik sertleşme, kalp hastalığı, Doppler ekokardiyografi, ailevi Akdeniz ateşi, ventrikül fonksiyon bozukluğu

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Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disease that occurs worldwide and predominantly affects populations of Mediterranean basin (1). Clinically, FMF is characterized by recurrent, acute, self-limiting attacks of fever and serositis, lasting at average 24-72 hours (2). Current evidence indicates that subclinical inflammation continues during attack-free periods of FMF (3, 4).

Clinical and subclinical cardiovascular involvement have been reported in several inflammatory rheumatic diseases including rheumatoid arthritis (RA) (5), ankylosing spondylitis (6), systemic lupus erythematosus (SLE) (7), and Behçet's disease (8). However, there is considerable lack of evidence regarding cardiac involvement in FMF patients.

As echocardiography is a reliable, cost-effective, non-invasive and reproducible diagnostic tool to evaluate aortic wall functional and anatomical alterations, cardiac function and structures, we aimed to investigate systolic and diastolic ventricular functions, aortic elastic properties and the presence of pericardial effusion in FMF patients by using conventional echocardiography and pulsed wave tissue Doppler imaging (TDI) methods.

Methods

This cross-sectional and case-control study was conducted between February and July 2006. Fifty-two out of 453 adult FMF patients, diagnosed in accordance with Tel-Hashomer criteria (9), registered in the computer files of our department all over the country, were included in the study. The patients living in city of İzmir who did not have a record regarding history of cardiac and pulmonary disease, diabetes mellitus, hypertension, hyperlipidemia and amyloidosis in the computer files were contacted for the study. We were able to contact 55 subjects and invited them to participate in the study. Thirty-three volunteers, with a similar age and sex distribution to the FMF patients, recruited from hospital staff. Same exclusion criteria were applied to controls as well as patients. None of the patients refused to join to the study. Eight of the FMF patients were excluded because of hypertension (four patients), hyperlipidemia (two patients) and diabetes mellitus according to the two-hour oral glucose tolerance test (OGTT) after our clinical evaluation. Six of the controls were also excluded because of hypertension (four subjects) and hyperlipidemia (two subjects). This study was approved by the local ethical committee and all participants gave written informed consents.

Echocardiographic studies were performed on the remaining 44 FMF patients [21 males/23 females; median age: 30 (19-47) years] and 27 healthy controls [12 males/15 females; median age: 29.5 (22-38) years]. All patients fulfilled the Tel-Hashomer criteria for FMF (9). All were on regular daily colchicine treatment and measurements of the study were performed during the attack free period (at least seven days). None of the participants had impaired glucose tolerance according to the OGTT and none of the patients had proteinuria on dipstick urinalysis. The median disease duration for FMF patients was 15.5 (1-45) years.

Blood pressure was measured by using mercury sphygmomanometer after 5 minutes of resting period and in the sitting position. Two readings were taken half an hour apart and the average value was calculated. Hypertension was defined as the mean systolic blood pressure ≥140 mmHg, and/or mean diastolic blood pressure ≥90 mmHg or if the subject was on antihypertensive medication.

Hyperlipidemia was defined as the total cholesterol level ≥240 mg/dl or low-density lipoprotein (LDL) cholesterol ≥160 mg/dl or triglyceride level ≥200 or the use of lipid lowering medication.

The diagnostic criterion of the American Diabetes Association based on the 75-g OGTT was used to define diabetes mellitus and glucose intolerance (10).

Participants who reported smoking at least one cigarette per day during the year before the study were classified as smokers.

Laboratory evaluation

In the morning, after an overnight fast, venous blood was sampled for the measurement of serum concentrations of glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, LDL cholesterol, triglycerides, standard C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Thereafter, a 75-g oral glucose load was administered to whole group and venepuncture was repeated 2 hours later for measurement of post-challenge serum glucose.

Echocardiographic Examination

The echocardiographic examinations were obtained by using Sonos 4500 (Hewlett Packard, USA) with a multifrequency transducer (2.5-4 MHz) equipped with TDI technology. Images were taken with subjects in left lateral decubitus position and Doppler measurements were obtained during end-expiration. All echocardiographic measurements were performed by a single experienced cardiologist throughout the whole study using the same device blinded to the study groups. M-mode traces were recorded at a speed of 50 mm/s and the Doppler signals at 100 mm/s and measurements of at least three cardiac cycles were averaged in sinus rhythm. The recorded echocardiography tracings were analyzed by another experienced cardiologist.

M-mode, two-dimensional and standard Doppler echocardiography

M-mode measurements were done according to the recommendations of the American Society of Echocardiography (11). Presence of pericardial effusion was evaluated from the posterior wall of the left ventricle at end-diastole and pericardial effusion was defined as ≥2 mm echo-free space between the pericardial layers of the left ventricle posterior wall. Valvular regurgitation was assessed qualitatively and graded as none, trace, mild, moderate, or severe by using color-coded Doppler imaging (12). Left ventricular ejection fraction was measured using the modified Simpson's method (13).

The sample volume (size 2 mm) of the pulsed wave Doppler was placed between the tips of the mitral leaflets in the apical four-chamber view. The mitral inflow velocity was traced and the following variables derived: peak velocity of early (E) and late (A) filling and deceleration time (DT) of the E wave velocity. Left ventricular isovolumic relaxation time (IVRT) was measured as the interval between aortic valve closure and the onset of

mitral flow. The ratio of early to late peak velocities (E/A) was calculated. Peak velocities of E and A wave and E/A ratio were also obtained for right ventricle in the apical four-chamber view, placing the sample volume at the tips of the tricuspid valve.

The propagation velocity of early flow into the left ventricle cavity (Vp) and tricuspid annular plane systolic excursion (TAPSE) were measured from the apical four-chamber view. The Vp was measured using color M-mode Doppler after aligning the cursor in the direction of inflow jet from the mitral annulus in the early diastole to 4 cm distally into the left ventricle cavity. To determine TAPSE, the M-mode cursor was oriented to the junction of the tricuspid valve plane with the right ventricle free wall using the apical 4-chamber view. The echoes generated were received and registered as motion of the right ventricle base. Maximal TAPSE was determined by the total excursion of the tricuspid annulus from its highest position after atrial ascent to the peak descent during ventricular systole.

Diameter of the ascending aorta was measured from the same view on the M-mode tracing at a level of 3 cm above the aortic valve. The systolic aortic diameter (AOS) was measured at the maximal anterior motion of the aorta, whereas the diastolic aortic diameter (AOD) was measured at the peak of the QRS complex on the simultaneously recorded electrocardiogram. Following parameters of the aortic elasticity were calculated according to the following formulas: The aortic strain (AOST) = [(AOS - AOD)/AOD], aortic stiffness (β) index=ln (systolic blood pressure/diastolic blood pressure)/AOST and aortic distensibility= 2xAOST/pulse pressure

Tissue Doppler echocardiography

The TDI was performed by activating the tissue Doppler function in the same echocardiography machine. In the apical four chamber view, a 5 mm pulsed Doppler sample volume was placed at the level of the lateral mitral and tricuspid valves. For each ventricle, myocardial systolic wave (Sm) velocity and the diastolic indices, myocardial early (Em) and atrial contraction (Am) peak velocities, were measured and Em/Am ratio was calculated.

The following parameters were used to define ventricular systolic and diastolic function:

1- Preserved left ventricular systolic function: LVEF≥ 55% (14).

2-Left ventricular diastolic dysfunction (conventional Doppler): E/A<50 years<1, or E/A>50 years<0.5, or IVRT<30 years>92 ms, or IVRT30-50 years>100 ms, or IVRT>50 years>105 (15).

3-Left ventricular diastolic dysfunction (TDI and conventional Doppler methods): Em/Am<1 (16), Vp<50 cm/s (17) or E/Em>15 (18, 19).

4-Right ventricular diastolic dysfunction (conventional Doppler): E/A<1.

5-Right ventricular diastolic dysfunction (TDI): Em/Am<1.

Reproducibility

To examine the reproducibility, ten healthy subjects were examined on two different occasions within a week. Intra-class correlation coefficients were substantial for right ventricular Em/Am, left ventricular E/A and right ventricular E/A ratios (0.74, 0.73 and 0.76, respectively). On the other hand, intra-class correlation coefficients of the left ventricular Em/Am ratio, Vp, TAPSE, systolic and diastolic aortic diameter measurements were excellent (0.85, 0.87, 0.84, 0.99 and 0.99 respectively).

Statistical analysis

The statistical analysis was carried out by using Statistical Package of Social Science (SPSS), version 13.0 (Chicago, IL, USA). Comparison between groups of continuous variables was performed by using the Mann-Whitney U test. Fisher's exact test was performed for the comparison of categorical variables. The Spearman rho correlation was used to determine relationships between parameters. The average intra-class correlation was used to assess the reproducibility of the echocardiographic assessment. A p value of <0.05 was considered as statistically significant.

Results

Clinical characteristics of the study group are presented in Table 1. There were 44 FMF patients (21 males/23 females) and 27 healthy controls (12 males/15 females). Age, sex, body mass index (BMI), smoking status and serum lipids were similar in FMF patients and control subjects (p>0.05). However, acute phase reactants (ESR and CRP) were significantly higher in the FMF patients compared to controls (p=0.04 and p=0.002, respectively). The median disease duration for FMF patients was 15.5 (1-45) years. The number of attacks before and after colchicine treatment was 15 (2-100) and 2 (0-36) per year respectively (p<0.001). Median daily colchicine use was 1.5 (0.5-2) grams.

Echocardiographic examination

None of the subjects had significant pericardial effusion or had moderate or severe valve abnormalities. Cardiac

Table 1. Clinical and laboratory characteristics of the subjects

Parameters	FMF patients (n=44)	Controls (n=27)	p
Age, years	30 (19-47)	29.5 (22-38)	0.31
Sex, M/F	21/23	12/15	0.81
Smoking , %	30	30	1
BMI, kg/m^2	23.4 (18.8-30.8)	22.2 (19.1-27.9)	0.81
BSA, m^2	1.7 (1.45-2.22)	1.78 (1.5-2.4)	0.28
Pulse pressure, mm/Hg	40 (20-62)	42 (33-64)	0.21
Fasting glucose, mg/dL	87 (72-104)	82 (67-105)	0.21
Second hour glucose, mg/dL	88 (45-170)	82 (44-154)	0.15
Total Cholesterol, mg/dL	160 (101-226)	178 (123-219)	0.37
LDL Cholesterol, mg/dL	87 (47-147)	98 (55-145)	0.67
HDL Cholesterol, mg/dL	49 (34-78)	55 (36-98)	0.06
Triglyceride, mg/dL	97 (43-184)	84 (39-188)	0.06
ESR, mm/h	10 (3-90)	8 (2-18)	0.04
CRP, mg/L	2.5 (0.3-65.8)	0.93 (0.2-8.6)	0.002

Continuous data are presented as median with minimum-maximal values
For the comparison of continuous variables, Mann–Whitney U test was used
For comparison of proportions, the Fisher's Exact Test was used
BMI- body mass index, BSA- body surface area, CRP- C-reactive protein, ESR- erythrocyte sedimentation rate, F- female, FMF- familial Mediterranean fever, HDL- high-density lipoprotein, LDL- low-density lipoprotein, M- male

dimensions, left ventricular mass index, fractional shortening percentage and left ventricular ejection fraction values were similar in FMF patients and controls (p>0.05). The data obtained from the M- mode and standard Doppler echocardiography (SDE) is summarized in Table 2 and TDI examination results are given in Table 3.

Left ventricle

Four subjects (two in FMF patients and two in controls; p>0.05) had left ventricular diastolic dysfunction (LVDD) diagnosed by standard Doppler echocardiography (15).

Color M-mode Doppler study revealed significantly lower values of Vp in the FMF patients compared to healthy subjects (p<0.008). On the other hand, when Vp < 50 cm/s accepted as a cut-off for LVDD (17), seven FMF patients and one control subject had LVDD (p>0.05) (Table 2).

Tissue Doppler imaging- parameters of mitral lateral annulus revealed significantly lower Em/Am ratios in the FMF patients group compared to controls (p=0.02). Six subjects (5 FMF patients vs. one control; p>0.05) had LVDD with Em/Am ratio of the mitral lateral valve <1 (Table 3).

Another index of LVDD, E/Em ratio, was not different between FMF patients and controls (p>0.05). In addition, there were no subjects who had E/Em ratio greater than 15.

Figure 1 represents diastolic dysfunction indices of left ventricle either obtained from TDI or color M -mode techniques.

Right ventricle

Right ventricular E/A ratio was similar between FMF patients and controls. Ten subjects had right ventricular diastolic dysfunction (RVDD) by SDE method according to the criteria E/A ratio <1; however, significance was not seen between the groups (7 FMF patients and 3 controls; p>0.05).

Tissue Doppler imaging examination of the tricuspid lateral valve indices in the patients including Em and Am peak velocities and Em/Am ratio were significantly different in FMF patients and controls (p=0.02, p=0.01, and p<0.001, respectively). There were 19 patients who had RVDD with Em/Am ratio <1. However, none of the controls had RVDD according to those criteria. When only the cases under the age of 50 were re-analyzed, Em/Am ratio <1 was present in 18 out of 41 patients (p<0.001) (Table 3).

The TAPSE was significantly reduced in the FMF patients (p<0.001) as compared with controls. Eight of the FMF patients and one healthy subject (p<0.025) had impaired TAPSE (<2 cm). The cases under the age of 50 years demonstrated similar findings (Table 2).

Table 2. M- mode, two-dimensional and standard Doppler echocardiographic data

Variables	FMF patients (n=44)	Controls (n=27)	p
Left atrial dimension, cm	3.4 (2.2-4.3)	3.2 (2.7-4.1)	0.7
LVDs, cm	3.1 (2.5-3.7)	2.9 (2.5-4)	0.83
LVDd, cm	4.6 (3.8-5.4)	4.7 (3.9-5.9)	0.38
IVS, cm	0.8 (0.5-1.2)	0.8 (0.6-1.2)	0.73
LVMI, g/m^2	82.8 (29.9-125)	74.3 (33-121.7)	0.45
FS, %	34 (15.9-44.4)	35.6 (19.6-44)	0.18
EF, %	66 (57-72)	65 (60-74)	0.84
Vp, cm/s	63 (39-100)	74 (40-94)	0.008*
Vp <50 cm/s	7	1	0.12
TAPSE, cm	2 (1.3-2.5)	2.5 (1.7-3.2)	
<0.001*			
TAPSE <2.0 cm	8	1	0.025*
Mitral inflow			
E peak velocity, cm/s	80 (50-110)	76.5 (60-110)	0.27
A peak velocity, cm/s	57 (30-80)	50 (40-70)	0.69
E/A ratio	1.4 (0.9-3)	1.47 (1-2.2)	0.52
IVRT, ms	75 (45-130)	77 (45-101)	0.94
E wave DT, ms	133 (65-210)	145 (110-196)	0.04*
Tricuspid inflow			
E peak velocity, cm/s	60 (30-90)	60 (40-87)	0.02
A peak velocity, cm/s	40 (23-86)	43 (30-80)	0.21
E/A ratio	1.4 (0.5-2.2)	1.4 (0.6-2.7)	0.47
Aortic elastance			
AOS, cm	3.1 (2.4-4.6)	3 (2.3-3.5)	0.08
AOD, cm	2.9 (1.9-4.5)	2.7 (2-3.4)	0.09
AOST, %	7.5 (1.3-41.3)	6.4 (1.2-28)	0.67
β index	5.4 (1.5-35.4)	7.9 (1.6-35.2)	0.53
Distensibility, 10-3/kPa	30.8 (4.2-126.3)	19.7 (4.3-102.4)	0.32

Continuous data are presented as median with minimum-maximal values
For the comparison of continuous variables, Mann–Whitney U test was used. For comparison of proportions, the Fisher's exact test was used
* All the significant p values remained significant when only those patients and controls under the age of 50 were analyzed
A- atrial contraction diastolic flow velocity, AOD- aortic diameter in diastole, AOS- aortic diameter in systole, AOST- aortic strain, , index - aortic stiffness index, DT- deceleration time, E- early diastolic flow velocity, EF- ejection fraction, FS- fractional shortening, IVRT- isovolumic relaxation time, IVS- wall thickness of interventricular septum, LVDd- left ventricular end-diastolic dimension, LVDs- left ventricular end-systolic dimension, LVMI- left ventricular mass index, TAPSE- tricuspid annular plane systolic excursion, Vp- the colour-M-mode slope of the early diastolic left ventricular filling phase (mitral flow propagation velocity)

Table 3. TDI analysis of left ventricular lateral mitral annulus and right ventricular tricuspid annulus

Variables	FMF patients (n=44)	Controls (n=27)	p
Mitral lateral annulus			
Em peak velocity, cm/s	18 (13-23)	17.4 (10-25)	0.99
Am peak velocity, cm/s	10 (6-17)	8 (4-21)	0.05
Sm peak velocity, cm/s	11 (9-17)	11.7 (3-16)	0.27
Em/Am ratio	1.77 (0.6-3.4)	1.79 (0.9-4.8)	0.02*
E/Em ratio	4.5 (2.2-6.7)	4.7 (3.2-9)	0.5
Em/Am<1, n	5	1	0.4
Tricuspid annulus			
Em peak velocity, cm/s	16 (10-23)	17.3 (13-25)	0.02*
Am peak velocity, cm/s	14 (9-21)	12 (6-19)	0.01*
Sm peak velocity, cm/s	15 (7-22)	14 (11-21)	0.2
Em/Am ratio	1.1 (0.7-1.9)	1.4 (1-2.5)	<0.001*
Em/Am<1, n	19	0	<0.001*

Continuous data are presented as median with minimum-maximal values
For the comparison of continuous variables, Mann-Whitney U test was used
For comparison of proportions, the Fisher's exact test was used
* All the significant p values remained significant when only those patients and controls under the age of 50 were analyzed
A- myocardial atrial contraction diastolic flow velocity, E- myocardial early diastolic flow velocity, TDI- tissue Doppler imaging

Box plot graphic of the right ventricular Em/Am ratio and TAPSE is given in Figure 2.

Aortic elasticity

The systolic and diastolic diameters of the aorta, aortic elastic properties and aortic distensibility were similar in FMF patients and controls (p>0.05) (Table 2).

Correlation analysis

Correlation analysis of the right ventricular Em/Am, representing RVDD, yielded significant correlations with TAPSE, CRP, triglyceride, BMI, Vp, left ventricular Em/Am ratio and left ventricular E/A ratio (p<0.001, r=0.5; p=0.01, r=-0.4; p=0.04, r= -0.3; p=0.007, r=-0.3; p=0.02, r=0.3; p<0.001, r=0.5 and, p=0.009, r=0.3 respectively).

Right ventricular systolic function index TAPSE was significantly correlated with right ventricular Em/Am ratio, ESR, CRP, AOST, aortic distensibility, FS% and Vp (p<0.001, r=0.5; p=0.01, r=-0.3; p=0.03, r=-0.3; p=0.04, r=-0.3; p=0.03, r= -0.3; p=0.005, r=0.4 and, p<0.001, r=0.6, respectively).

Left ventricular Em/Am ratio, representing LVDD, showed significant correlations with left ventricular E/A ratio, right ventricular Em/Am ratio, age, fasting blood glucose, BMI, triglyceride, Vp and colchicine dose (p<0.001, r=0.5; p<0.001, r=0.5; p<0.001, r=-0.4; p=0.04, r=-0.2; p=0.03, r=-0.3; p=0.02, r=-0.3; p=0.03, r=0.3, and p=0.03, r=0.3, respectively).

Mitral flow propagation velocity, representing LVDD, was correlated significantly with left ventricular E/A ratio, left ventricular Em/Am ratio, pulse pressure and right ventricular Em/Am ratio (p=0.02, r=0.3; p=0.03, r= 0.3; p=0.04, r=0.4, and p=0.02, r=0.3, respectively).

Other parameters including disease duration, numbers of attacks before and after colchicine treatment were not correlated with left and right ventricular Em/Am ratio, TAPSE and Vp.

Discussion

The results of our study demonstrate that systolic and diastolic functions of right ventricle and diastolic function of left ventricle are impaired in patients with FMF when compared to healthy controls. On the other hand aortic elastic properties and pericardium showed no significant difference between groups.

There are several anatomic sites such as the pericardium, aorta, myocardium and the cardiac conduction system, which may be involved in various rheumatic diseases. However, there is a considerable lack of evidence regarding cardiac involvement in FMF patients. The disease of pericardium, although it is a double-layered serous membrane, is a rare manifestation of FMF. In a series of 2468 patients, only 34 subjects (1.4%) had pericarditis (20). In another study, the incidence of pericardial effusion was 3.6% during attacks of FMF (21). The present study, which investigates pericardial effusion during attack free period of FMF shows that pericardium is not affected in FMF patients during the attack free periods.

Myocardial involvement, especially LVDD, is a relatively common problem among patients with inflammatory rheumatic conditions. Up to 44% of ankylosing spondylitis (22), 66% of RA (23), 40% of Behçet's disease (24), and 64% of SLE patients (25) may have LVDD. In addition, right ventricular diastolic impairment has also been reported in the above disorders (26-29). Several mechanisms have been proposed as a cause of diastolic dysfunction in inflammatory rheumatic diseases such as the fibrous scarring of the heart muscle, abnormal myocardial collagen deposition, myocardial infarcts, focal inflammation, vasculitis, myocarditis, arteritis and amyloidosis (7, 26, 27, 30, 31). The presence of asymptomatic diastolic dysfunction in RA and SLE patients is believed to be partly responsible for the increased cardiovascular mortality (23, 25).

Diastolic dysfunction can be identified by standard echocardiography and/or recently introduced methods such as TDI. Standard echocardiography has several limitations; one major limitation is its dependence of loading conditions and heart rate for the assessment of diastolic ventricular function (32). In case of worsening left ventricular diastolic function there is a compensatory increase in left atrial pressure resulting in an increase in E wave velocity of the mitral inflow and therefore pseudo-normalization of the filling pattern (normal E/A ratio and DT) (33). The TDI is a new technique, which offers useful information about ventricular functions (19). Myocardial or annular velocities are easy to obtain, volume-load independent and offer a rapid way to differentiate normal from pseudo-normal pattern and constrictive from restrictive pathology (16, 19, 33). Another preferred method for assessing left ventricular diastolic function is the measurement of Vp by color M-mode echocardiography (34). This method is also volume independent and decreased Vp (<50 cm/s) could reliably detect all grades of diastolic dysfunction (17).

In this study, standard echocardiography revealed similar results for FMF patients and controls regarding LVDD. However, TDI study and color M-mode investigations of the left ventricle showed significant difference between the FMF patients and

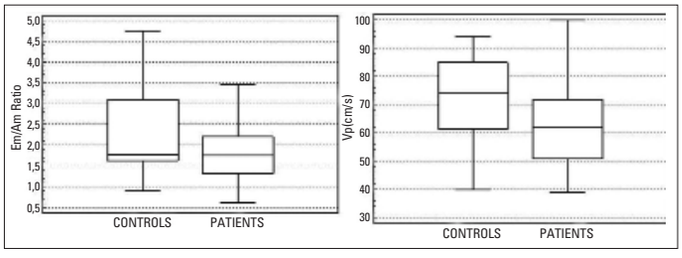

Figure 1. Boxplot graphic of the left ventricular diastolic dysfunction indices: Em/Am ratio and Vp

Am- mitral annular atrial contraction velocity, Em- mitral annular early diastolic velocity, Vp- mitral flow propagation velocity

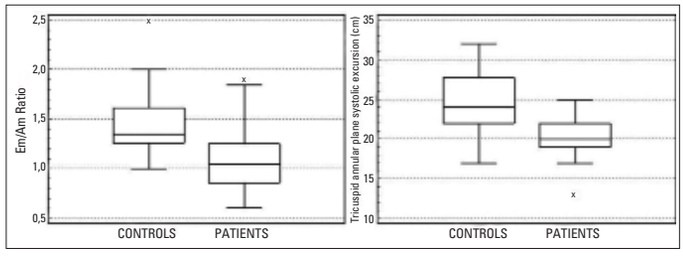

Figure 2. Boxplot graphic of the right ventricular diastolic and systolic indices: Em/Am ratio and TAPSE

Am- tricuspid annular atrial contraction velocity, Em- tricuspid annular early diastolic velocity, TAPSE- tricuspid annular plane systolic excursion

control groups regarding Em/Am and Vp values but not in E/Em values. The number of subjects who had Em/Am<1, Vp<50 cm/s and E/Em>15 were similar in the groups. Although these criteria of LVDD were not completely met in FMF patients; the significantly lower values of Em/Am and significantly reduced Vp values suggest the LVDD in a cohort of relatively young FMF patients who were free of classical cardiovascular risk factors.

Measurements of right ventricular functions are difficult due to the complex three-dimensional structure and nonconcentric contraction of this ventricle (35). In addition, conventional Doppler studies conducted for RVDD have the same limitations for left ventricle, like its dependence of preload, afterload and heart rate (32). The TDI method has been shown to be superior when compared to standard Doppler in assessing RVDD (36). In the present study, we found no difference regarding RVDD by using standard Doppler echocardiography. In FMF patients, there was a pronounced right ventricular diastolic dysfunction detected with TDI method. Both the number of FMF patients with Em/Am<1 and Em/Am ratio were significantly different from healthy subjects. The TAPSE is a simple, reproducible and accurate index of right ventricular systolic function (37) and a cut-off value of TAPSE< 2 cm could identify patients with some degree of either right or left ventricular systolic dysfunction (38). In this study, FMF patients also exhibited a significantly depressed TAPSE value. Furthermore, the number of FMF patients with TAPSE< 2 cm was also significantly higher than the healthy controls. As none of the patients and controls had impaired left ventricular systolic function described by a normal ejection fraction, the depressed values of TAPSE may indicate a subclinical right ventricular systolic dysfunction in FMF.

There are a few of studies investigating cardiac and vascular functions in adult patients with FMF. An impaired endothelial function, a key early event in atherosclerosis (39), has been reported in FMF patients (40). However, another study investigating early atherosclerosis in adult patients with FMF did not report endothelial dysfunction (41). There are also two recent studies investigating cardiac functions in FMF (42, 43). Tavil et al. (43) studied 30 cases and showed significantly reduced left ventricular Em/Am ratio in FMF patients. However, myocardial performance index reported to be unchanged. Other parameters including right ventricular Em/Am ratio and TAPSE were depressed in FMF group but missed significance. This is probably due to the lower number of subjects in the patients group and may explain the difference between our findings and those of Tavil et al. (43). In the second study, Caliskan et al. showed impaired coronary microvascular function in FMF patients by using echocardiography. In the same study left ventricular E/A ratio and isovolumic relaxation time of FMF patients were significantly different from healthy controls by using standard Doppler echocardiography. Interestingly, TDI examination of these subjects revealed no difference regarding LVDD between FMF patients and controls (42). However, both studies did not mention the number of subjects who had diastolic dysfunction according to the established criteria and made their conclusions only using the comparisons of E/A or Em/Am ratios between groups.

Aortic stiffness was reported to be a predictor of cardiovascular morbidity and mortality and can be assessed by noninvasive methods (44). Inflammation and disease related factors may cause aortic damage in autoimmune rheumatic diseases. In this context, impaired aortic mechanical properties have been reported in patients with SLE (45), Behçet's disease (30), and ankylosing spondylitis (46). A recent study including 31 FMF patients has also reported abnormal aortic stiffness parameters (47). In contrast to that study our results failed to demonstrate impaired elastic properties of the aorta (calculated from the AOST, index and aortic distensibility) in FMF patients compared to healthy controls. It is well known that aging is associated with impaired aortic elasticity (44) and one possible explanation for this discrepancy between our study and previous study may be related to the younger age of our patients (median 30 years compared to 37 years) (47).

In the present study, we excluded subjects with hypertension, diabetes mellitus, dyslipidemia, cardiac and pulmonary problems to avoid the negative effects of these variables on myocardium. In addition, the number of smoking subjects was similar between groups. We also analyzed subjects under fifty years of age and the subgroup analysis revealed the same findings. Thus, the abnormal findings of left ventricular diastolic and right ventricular systolic and diastolic functions are due to disease-related factors. Furthermore, correlation of right ventricular Em/Am ratio and TAPSE with CRP may support the role of inflammation in the myocardial dysfunction.

Limitations of the study

One limitation of this study is that we did not perform invasive methods to assess aortic elasticity and pulse pressure. Although invasive methods are still the gold standards, several reports demonstrated that M-mode echocar-diography is a reliable alternative to invasive techniques. Indeed, non-invasively calculated aortic elasticity showed excellent correlation with the indices derived from the invasive methods (44, 48). The other limitations of this study are as follows; the absence of patients not receiving colchicine and the absence of patients with acute attacks of FMF. Therefore, further studies include such patients are needed to confirm our results.

Conclusions

Our results suggest that subclinical myocardial involvement is present in patients with FMF, whereas pericardium and aorta seem to be spared during attack free periods.

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