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Assessment of Myocardial Function in Patients With Fibromyalgia and the Relationship to Chronic Emotional and Physical Stress

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ABSTRACT

Background and Objectives: An association between emotional or physical stressful triggers and adverse cardiovascular events, such as death and myocardial infarction, has been recognized for many years. The clinical features of transient left apical ballooning syndrome have been clearly described, but the effect of chronic stress on the myocardium is unknown. Our objective was to assess left ventricular (LV) function in patients with fibromyalgia *(FM) with chronic emotional and physical stress*. **Subjects and Methods**: We investigated 30 consecutive postmenopausal women (mean age, 48±8 years) satisfying the criteria for FM with atypical chest pain and 20 age-matched healthy controls by means of standard and 2-dimensional strain (2DS) echocardiography. Patients with hypertension, coronary heart disease, or diabetes were excluded. Global and segmental longitudinal deformation parameters of LV function from 3 apical views were analyzed, and patients underwent a manual tender point survey for the number of tender points and tender point counts, and completed the Fibromyalgia Impact Questionnaire (FIQ), which was comprised of physical and feel scores, the Brief Fatigue Inventory (BFI), and the Beck Depression Inventory (BDI). **Results**: Both global and segmental longitudinal LV strains were significantly reduced in FM patients with high FIQ scores (>50) compared to FM patients with low FIQ scores (-18.98% vs. -22.72%). Various emotional and physical stress indexes were significantly correlated with global LV strain. **Conclusion**: Global and segmental LV strains were negatively associated with fatigue, tender point count, and FIQ score. However, there was no significant association between depression and LV strain. This study demonstrated that chronic emotional or physical stress in FM patients might reduce myocardial longitudinal deformation. **(Korean Circ J 2010;40:74-80)**

KEY WORDS: Fibromyalgia; Emotional stress; Echocardiography; Strains.

Introduction

Physical or emotional stress has long been known to have an impact on the cardiovascular system. Reversible electrocardiographic and echocardiographic changes have been reported in patients under emotional stress[1)2)] or physical stress,[3)] including non-cardiac illnesses. Acute stress with catecholamine release has numerous well-known effects on the cardiovascular system, including increased heart rate, cardiac output, and peripheral vascular constriction, leading to a short-term increase in blood pressure. Chronic stress is thought to contribute to the risks for cardiovascular disease through persistent activation of the sympathetic nervous system and Hypothalamic-pituitary-adrenal (HPA) axis.[4)] Brief mental stress can cause transient endothelial dysfunction in healthy individuals.[5)6)] In animal models, psychologic stress produces actual endothelial injury[7)8)] and chronic cardiovascular stimulation can also lead to vascular hypertrophy and chronically elevated blood pressure.

Fibromyalgia (FM) is characterized by widespread musculoskeletal pain lasting at least 3 months with discrete points of tenderness (>11 of 18 sites).[9)] Patients with FM experience a variety of other symptoms, including sleep disturbance, fatigue, stiffness, cognitive dysfunction, and non-cardiac chest pain. There is an over-

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lap between FM and depression, and the correlation between coronary heart disease and depression is documented. Also, there is a study which has demonstrated a significantly higher proportion of FM, an increased level of tenderness to touch, and higher scores on the Fibromyalgia Impact Questionnaire (FIQ) scale among patients with pathologic findings on coronary angiography.[10] Several studies have shown that beliefs or perceptions regarding pain may influence the intensity of pain,[11)12] and patients who have perceptions of catastrophic illness experience more pain, feel more disabled by their pain, suffer more psychologic distress, and have poor outcomes following pain treatment.[13] The aim of the present study was to determine myocardial function in patients with FM with 2-dimensional strain (2DS) echocardiography, and to examine the relationship between chronic mental and physical stress and myocardial function.

Subjects and Methods

Study population

The study was approved by the Maryknoll Medical Center Institutional Review Board. FM patients with atypical chest pain were recruited from the Rheumatology and Cardiology Services at the Maryknoll Medical Center between September 2008 and March 2009. Participants were selected according to the following criteria: postmenopausal and experiencing pain from FM at the time they completed the survey. The patients then received informed consent according to Institutional Review Board guidelines and a set of questionnaires. The echocardiographic examination was obtained after the survey, and an exercise stress test was performed to exclude ischemic heart disease.

The control group included 20 age-matched healthy postmenopausal females with normal echocardiograms and exercise stress tests. Patients were excluded for the following reasons: hypertension, coronary artery disease (CAD), diabetes mellitus, significant valvular heart disease, advanced arrhythmia, and the inability to provide informed consent.

Assessments

To provide confirmation of FM, a clinical examination was performed by a rheumatologist in which the 1990 American College of Rheumatology (ACR) criteria were applied. Subjects had to have at least 11 of 18 tender points and widespread musculoskeletal pain, above and below the waist, of 3 months' duration or longer to qualify for entry into the research program.

During the survey, all participants completed the FIQ, an Index of change in FM-related symptomatology, which correlates with the degree of disability.[14] The Korean version of the FIQ is comprised of 10 questions.[15] The first question contains 11 items related to the ability to perform large muscle tasks; each question is rated on a 4-point scale. Items 2 and 3 ask the patient to mark the number of days they felt well and the number of days they were unable to work (including housework) because of FM symptoms. Items 4 through 10 are horizontal linear scales marked in 10 increments on which the patient rates work difficulty, pain, fatigue, morning tiredness, stiffness, anxiety, and depression. The FIQ is a self-administered instrument that takes approximately 3-5 minutes to complete. The directions are simple and the scoring is self-explanatory, so a higher score indicates a greater impact of the syndrome on the person. Each of the 10 items has a maximum possible score of 10, thus the maximum possible score is 100. The average FM patient scores about 50; severely afflicted patients usually score ≥ 70. The study participants were divided 2 groups based on whether the FIQ score was >50 (group A) or <50 (group B).

The self-administered questionnaires, the Beck Depression Inventory (BDI) scale and the Brief Fatigue Inventory (BFI), assess symptoms of depression and fatigue, respectively. The BDI evaluates 21 symptoms of depression; 14 cognitive-affective symptoms and 7 somatic symptoms. Each symptom is rated on a 4-point intensity scale and scores are added to give a total ranging from 0-63. The higher scores represent more severe depression. A BFI consists of 9 items; fatigue and its interference are measured on numeric scales from 0-10. The global score for the BFI is calculated as the mean value of these 9 items. Severity of fatigue can be categorized as mild, moderate, or severe, as follows: 1-3, mild; 4-6, moderate; and 7-10, severe fatigue. Detailed demographic data were collected from medical records or participant interviews and included age, race, gender, marital status, concomitant illnesses, vital signs, physical examination results, and medications.

Echocardiographic evaluation

A standard 2DS echocardiographic examination was performed on all subjects lying in the left lateral supine position using a 3.5-MHz transducer on Vivid 7 Dimension ultrasound equipment (General Electric, Horten, Norway). Two-dimensional grayscale imaging (frame rate ≥ 70s) and color Doppler tissue imaging (frame rate ≥ 115s) were performed in the apical 2-, 3-, and 4-chamber views using a narrow sector angle. Images from the apical chamber views of the left ventricle (LV) were obtained at end-expiratory apnea and were stored in cineloop format for subsequent offline analysis. Three heartbeats were collected from each view and the selected 1-cycle was analyzed off-line with an Echo PAC Dimension system (General Electric). Peak systolic strains were measured and averaged to assess global longitudinal myocardial regional function (GLS). The endocardial borders were traced at the end-systolic frame, and an automated tracking algorithm outlined the myocardium in successive frames throughout the cardiac cycle.

The tracking quality was verified for each segment (with subsequent manual adjustment of the region of interest, if necessary), and myocardial motion was analyzed by speckle tracking within the region of interest bound by endocardial and epicardial borders. Inadequate tracked segments were automatically excluded from analysis. In this situation, the local strain in each segment was calculated. GLS was obtained by averaging all segment strain values from the apical 4-chamber, 2-chamber, and long axis views.

Statistical analysis

All data are expressed as the mean±standard deviation. Data were analyzed using standard statistical software {Statistical Package for the Social Sciences (SPSS) package, version 11.0; SPSS, Inc., Chicago, IL, USA} and comparisons of all measurements were made with paired Student's t-test for continuous variables and the Pearson correlation test for correlation. A $p<0.05$ indicated statistical significance.

Results

General characteristics of patients

The major demographic and clinical characteristics are given in Table 1. The mean age was 48±8 years (range, 42-66 years), and global LV systolic function, LV chamber dimension, and wall thickness were normal in all patients with fibromyalgia syndrome. The disease duration, number of tender points, and BDI showed no differences between the groups. However, the physical score, feel score, tender point counts, and BFI were significantly higher in the high FIQ score group (group A, n=20) than the low FIQ score group (group B, n=10) (Table 2).

Table 1. Baseline demographic characteristics of FMS patients and controls

	Group A (n=20)	Group B (n=10)	Control (n=20)
Age (years)	48.4±8.7	46.8±7.9	45.6±8.6
BMI (kg/m^2)	23.8±3.5	23.1±3.8	23.8±4.8
Systolic BP (mmHg)	124.4±14.0	127.4±12.8	123.8±11.9
Diastolic BP (mmHg)	78.1±7.7	76.1±8.3	76.2±9.3
HR (bpm)	72.8±8.7	73.9±6.7	74.1±5.8
Hemoglobin	12.3±1.4	12.1±1.7	12.4±1.5
Serum creatinine	0.7±0.32	0.8±0.27	0.8±0.34
Disease duration after diagnosis (years)	3.57±4.71	3.75±2.75	0

All values are described as the mean±SD. FMS: fibromyalgia syndrome, BMI: Body Mass Index, BP: blood pressure, HR: heart rate

Strain echocardiographic findings

There were no significant differences in the mitral inflow parameters and myocardial performance index (Tei index) between the groups (Table 3). However, significant decreases were noted in the values of global LV strain (GLS) of group A versus group B (-18.61±3.09% vs. -22.72±1.38%, p=0.001), specifically a lower mean systolic strain of the apical 4-chamber view (-18.21±3.05% vs. -22.88±1.63%, p=0.001), mean systolic strain of the apical 2-chamber view (-18.98±3.24% vs. -22.44±1.38%, p=0.002), and mean peak systolic strain of the apical long axis view (-18.32±3.42% vs. -22.72±1.75%, p=0.002) (Figs. 1 and 2) (Table 4). The FIQ score had a strong correlation with global and segmental LV strain (Fig. 3). The physical and feel scores of the FIQ also demonstrated significant correlations with the corresponding GLS (0.58 and 0.42 respectively, $p<0.05$). The value of the GLS correlated robustly with the 10 items of the FIQ, the highest correlations being with tender point counts (r=0.52), missed work (r=0.49), anxiety (r=0.49), and fatigue (r=0.49). The scale of the GLS also showed a strong correlation with the Tei index (r=0.72, p=0.007). The number of tender points and depression generally showed a poor correlation with GLS. Inter- and intraobserver variability was tested by independent analysis

Table 2. Comparisons of clinical variables between the FMS patients

	Group A (n=20)	Group B (n=10)	p
Physical impairment subscale	11.75±8.2	4.8±4.9	0.035
Feel good subscale	8.64±3.31	5.14±1.28	0.003
Work missed subscale	52.25±10.19	23.0±7.48	0.0001
Number of tender points	14.5±2.11	13.4±5.36	0.463
Tender point counts	31.95±7.13	22.80±7.72	0.019
Fatigue subscale (BFI)	57.7±17.1	30.0±13.98	0.006
Anxiety subscale	27.8±3.56	24.4±4.78	0.578
Depression subscale (BDI)	44.05±19.63	29.6±3.58	0.12

All values are described as the mean±SD. FMS: fibromyalgia syndrome, BFI: brief fatigue inventory, BDI: beck depression inventory

Table 3. Parameters of 2-dimensional echocardiography between the FMS patients and controls

	Group A (n=20)	Group B (n=10)	Control (n=20)
LVEDd (mm)	46.02±3.72	44.34±1.35	45.45±2.25
FS	35.45±2.68	35.00±1.58	34.75±2.19
EF (%)	65.00±2.90	63.78±3.06	67.8±9.5
RWT	0.42±0.04	0.41±0.03	0.39±0.7
LVMI (g/m^2)	94.8±18.06	88.40±8.96	90.1±12.7
LAD (mm)	37.94±2.85	35.22±1.61	36.18±1.93
Tei index	0.33±0.63	0.28±0.90	0.32±0.78

All values are described as the mean±SD. FMS: fibromyalgia syndrome, LVEDd: left ventricular end diastolic dimension, FS: fractional shortening, EF: ejection fraction, RWT: relative wall thickness, LVMI: left ventricular mass index, LAD: left atrial dimension

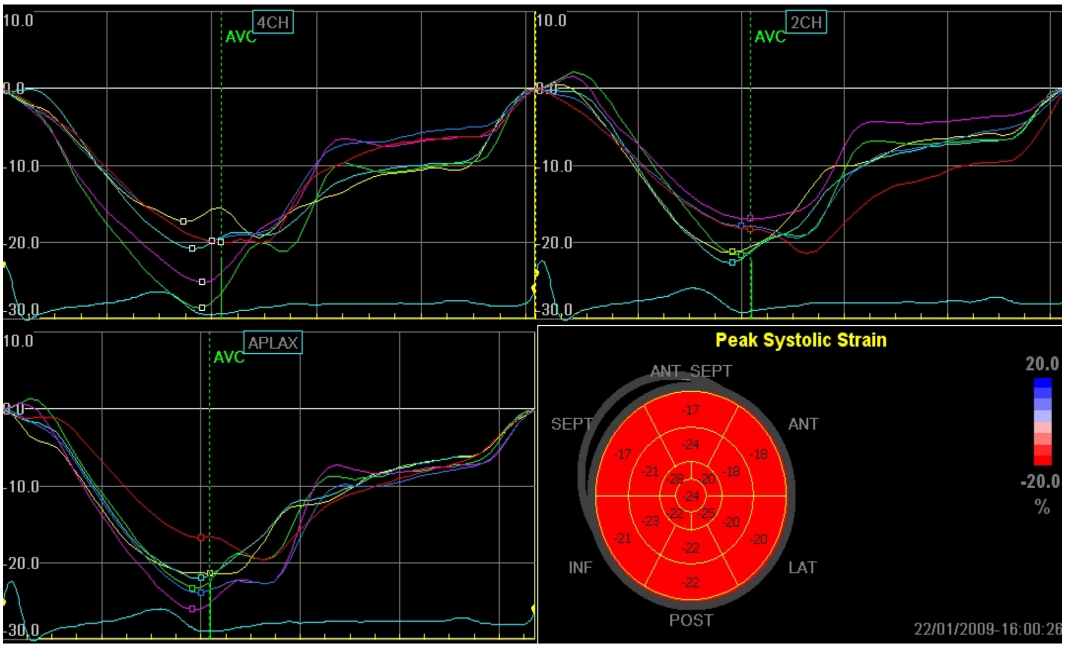

Fig. 1. A case of longitudinal strain analysis in patients with FMS and a low FIQ score by 2-dimensional speckle tracking strain analysis, which showed normal segmental and global left ventricular strain. FMS: fibromyalgia syndrome, FIQ: Fibromyalgia Impact Questionnaire.

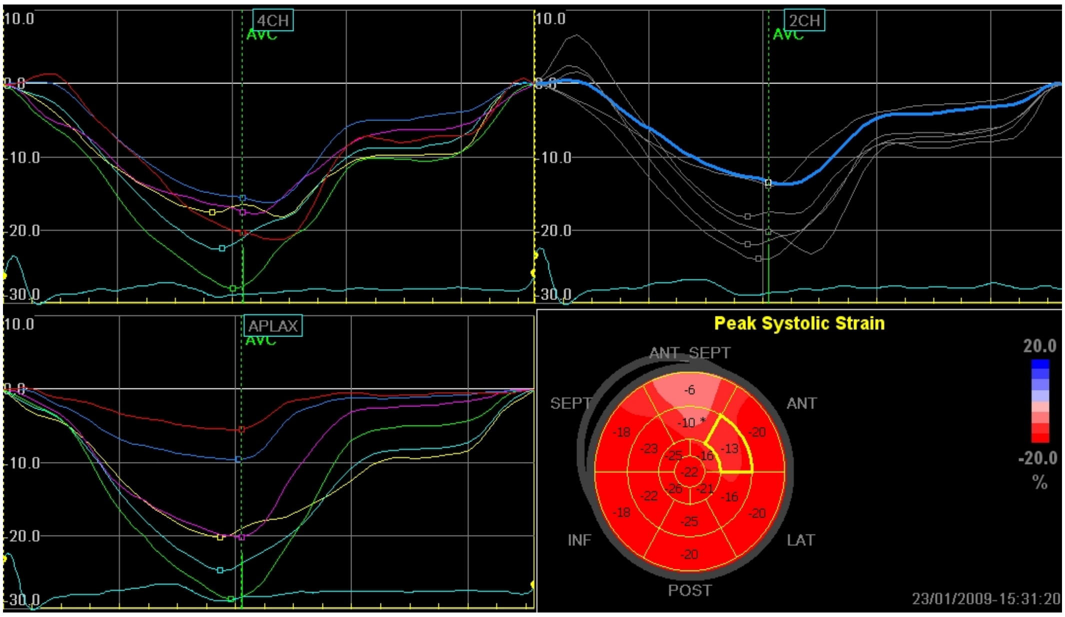

Fig. 2. A case of longitudinal strain analysis in patients with FMS and a high FIQ score by 2-dimensional speckle tracking strain analysis, which showed abnormal segmental and global left ventricular strain. FMS: fibromyalgia syndrome, FIQ: fibromyalgia impact questionnaire.

by two independent observers (C.K.I and L.S.H.) and by repeated measurement of these segments on another occasion by the same observer (C.K.I.). The interobserver variability was <12% and the intraobserver variability was 8%. The main reason for interobserver variability was a different location of the sample volume. Once sample volume was placed on a mutually agreed location within the myocardium, the measurements became virtually identical.

Discussion

The relationship between psychosocial factors, such as stress and CAD, has drawn significant attention. Chronically stressful situations, such as work stress, marital stress, caregiver strain, low social support, and low socioeconomic status, have been linked to an increased risk of CAD and adverse cardiac events.[18] There is also evidence that emotional stressors can act as trig-

Table 4. Parameters of mitral inflow pattern and strain between the FMS patients

	Group A (n=20)	Group B (n=10)	Control (n=20)
E velocity (cm/sec)	72.25±14.03	75.40±19.04	74.45±12.32
A velocity (cm/sec)	69.70±10.61	70.20±6.91	68.78±9.29
E/Ea	8.81±2.04	8.71±0.93	7.92±1.52
Peak systolic strain, LAX (%)	-18.32±3.42*†	-22.72±1.75	-21.63±4.21
Peak systolic strain, A4C (%)	-18.21±3.05*†	-22.88±1.63	-24.22±6.82
Peak early diastolic strain, A2C (%)	-18.98±3.24*†	-22.44±1.38	-23.35±6.46
Global LV strain (%)	-18.61±3.09*†	-22.72±1.46	-22.82±9.62

All values are described as the mean±SD. *$p<0.05$ vs. group B, †$p<0.05$ vs. control. FMS: fibromyalgia syndrome, E: peak early velocity, A: peak atrial velocity, Ea: early diastolic mitral annular velocity, LAX: apical long axis view, A4C: apical 4-chamber view, A2C: apical 2-chamber view, LV: left ventricular

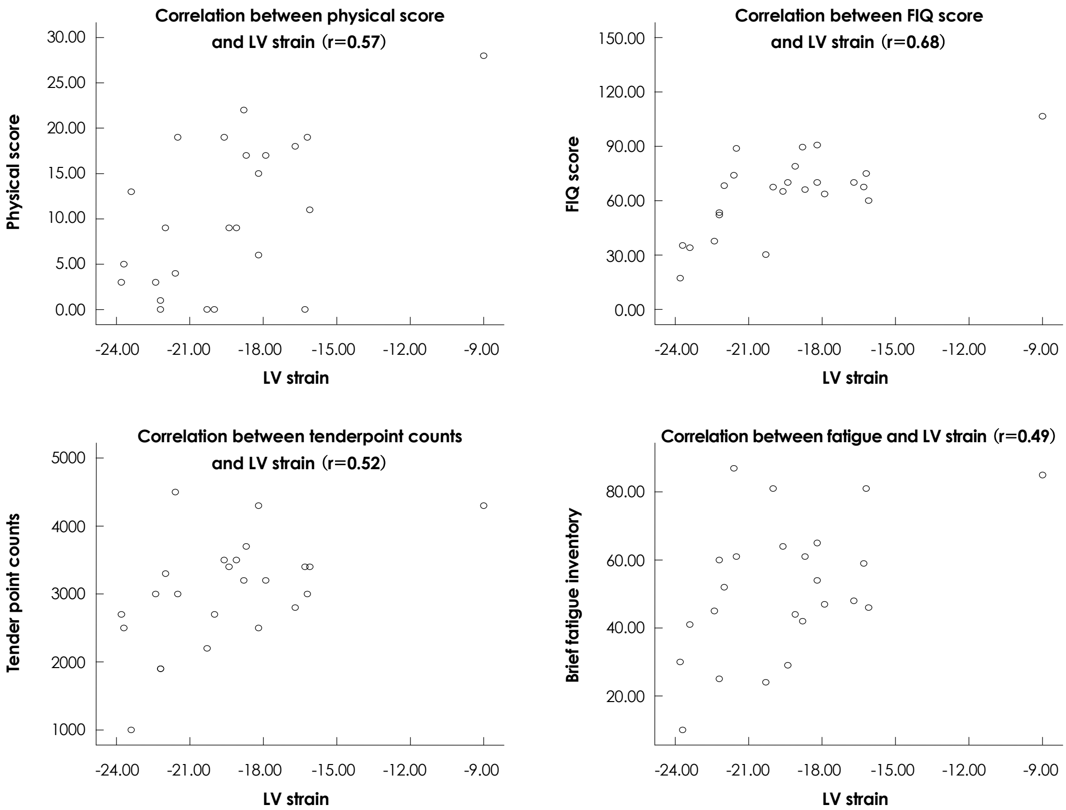

Fig. 3. Correlation between parameters of stress and global left ventricular strain (GLS). The value of the GLS showed modest negative correlation with parameters of physical stress score, Fibromyalgia Impact Questionnaire (FIQ), tender point counts, and fatigue (all $p<0.01$).

gers for acute cardiovascular events.[19] The present study tested the hypothesis that chronic stress may exert negative effects on LV function in patients with FM. The physical definition of strain is the relative change in length of a material related to its original length. The strain rate is the temporal derivative of the strain and so it expresses the local dynamics of myocardial performance. The longitudinal systolic strain rate has been shown to be linearly correlated with the maximal value of the first LV pressure time derivative and also with the peak elastance, which are both global measures of LV systolic function and contractility. The 2DS measurements, as determined by speckle tracking, have recently been used for the quantitative evaluation of LV function, and this method has been validated for the evaluation of longitudinal function.[20] Subclinical LV dysfunction relates to the structure-function relationship and characterizes a preclinical stage of myocardial damage that can be detected by a decrease in longitudinal myocardial function, the vulnerability of subendocardial fibers, that occurs before the development of abnormalities in conventional measures of LV performance, such as LV ejection fraction.[16] The main findings of this study were that global and segmental longitudinal LV strains were significantly reduced in FM patients with high FIQ scores than patients with low FIQ scores, despite comparable radial LV contraction parameters, such as ejection fraction and fractional shortening, implicating subclinical LV dysfunction. Although insignificant reductions in the ejection fraction and Tei index were observed in patients with FM with high FIQ scores, the Tei index was significantly correlated with LV strain. Both global and segmental LV strain was negatively associated with fatigue, anxiety, tender point count, and FIQ score. However, there was no significant association between depression and LV strain. This study demonstrated that severity of emotional or physical distress in patients with FM might be correlated with LV function and chronic distress might reduce myocardial longitudinal deformation by possible microcirculatory impairment or endothelial dysfunction due to excess activation of the sympathetic nervous system. Several mechanisms concomitant with or downstream to sympathetic nervous system activation have been proposed. Recent data suggest that elevated systemic levels of catecholamines are central to the pathophysiology of this disorder.[21] Catecholamines have been known to exert a toxic effect on the myocardium. Excessive catecholamine production in patients with pheochromocytoma induces reversible LV dysfunction analogous to tako-tsubo-like LV dysfunction.[22] The exact mechanism of catecholamine-induced myocardial damage, however, is thought to be multifactorial. Postulated mechanisms include persistent activation of calcium channels, membrane damage, and microvascular spasm.[23] Microvascular endothelial dysfunction can sensitize the coronary circulation to the vasoconstrictor effects of catecholamines.[24] Microvascular spasm and cardiac syndrome X are also associated with female predominance, particularly in the postmenopausal years,[25][26] congruent with the gender differences which exist in transient LV dysfunction. In the peripheral circulation, microvascular abnormalities are exacerbated by sympathetic nerve activation.[27] Given the association with physical or emotional stress in patients with transient LV dysfunction, chronic stress may play a role in changes in LV function. In this study, we have found, for the first time, myocardial longitudinal deformation assessed by 2DS echocardiography was reduced in patients with FM with chronic emotional or physical stress. Considering the good correlation between stress parameters and LV strain, further clinical evaluation of LV function with long-term follow-up is warranted, especially for the patients with FM and a high FIQ score.

This study had some limitations that should be considered. We did not evaluate the strain rate because this could not be obtained using automated function imaging software. However, as strain is a fundamental parameter that can be directly measured using the speckle tracking method, it might be a more relevant parameter than the strain rate.[28] Second, there was no significant difference in LV strain between patients with FM with a low FIQ score and age-matched healthy controls. The absence of a difference might be because the amount of stress was not severe enough to induce a change in LV function or FM patients with a low FIQ scorewere not susceptible to stress. However, whether the findings of reduced LV longitudinal deformation in FM patients with a high FIQ score is due to stress itself or disease characteristics are not convincing. As our present study was a cross-section study and the study population was small, a further prospective study will be required. Finally, the possible mechanism of observed LV dysfunction in FM patients with a high FIQ score was not investigated in this study, so a study focusing on vascular and endothelial function, such as brachial artery flow-mediated dilation by ultrasound and measurement of systemic levels of catecholamines will also be required.

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