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.

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 or physical stress, 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. Brief mental stress can cause transient endothelial dysfunction in healthy individuals. In animal models, psychologic stress produces actual endothelial injury 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). 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-
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. Several studies have shown that beliefs or perceptions regarding pain may influence the intensity of pain, 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. 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 due to their pain, suffering more psychologic distress, and have poor outcomes following pain treatment. 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, comorbid 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 cine-loop 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 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).
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 I. 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 (㎏/m²)          | 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    | 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

### 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 ± 3.11   | 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: 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 (mm)            | 0.42 ± 0.04    | 0.41 ± 0.03    | 0.39 ± 0.7    |
| LVMI (g/m²)         | 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

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 tendon 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 intra-observer variability was tested by independent analysis.
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. There is also evidence that emotional stressors can act as trig-
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. 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. 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 strain.

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

| Parameter                        | 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.
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) 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 score were 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.

REFERENCES

1) Brandspiegel HZ, Marinehak RA, Rials SJ, Kowey PR. A broken heart. Circulation 1998;98:1349.
2) Lee HH, Gwon HC, Kim BJ, et al. Clinical manifestation of novel stress-induced cardiomyopathy mimicking acute myocardial infarction: single center prospective registry. Korean Circ J 2002;32:1054-63.
3) Sharkey SW, Shear W, Hodges M, Herzog CA. Reversible myocardial contraction abnormalities in patients with an acute noncardiac illness. Chest 1998;114:98-105.
4) McEwen BS. Protective and damaging effects of stress mediators: central role of the brain. Dialogues Clin Neurosci 2006;8:367-81.
5) Ghiadioli L, Donald AE, Copley M, et al. Mental stress induces transient endothelial dysfunction in humans. Circulation 2000;102:2473-8.
6) Speicker LE, Burlilman D, Ruchitzka F, et al. Mental stress induces prolonged endothelial dysfunction via endothelin-A receptors. Circulation 2002;105:2817-20.
7) Henry JP, Ely DL, Stephens PM, Ratcliffe H, Sanishteban G, Shapiro AP. The role of psychosocial factors in the development of arteriosclerosis in CBA mice: observations on the heart, kidney, and aorta. Atherosclerosis 1971;14:203-18.
8) Straw WB, Bondjers G, Kaplan JR, et al. Endothelial dysfunction in response to psychosocial stress in monkeys. Circ Res 1991;68:1270-9.
9) Lawrence RC, Helmick CG, Arnett FC, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. Arthritis Rheum 1998;41:778-99.
10) Ablin JN, Beilinson N, Aloush V, Elkayam O, Finkelstein A. Association between fibromyalgia and coronary heart disease and coronary catheterization. Clin Cardiol 2009;32:E7-11.
11) Amtz A, Claassens L. The meaning of pain influences its experiences intensity. Pain 2004;109:20-5.
12) Lame IE, Peters ML, Vlaeyen JW, van Kleeve M, Putijn J. Quality of life in chronic pain is more associated with beliefs about pain, than with pain intensity. Eur J Pain 2005;9:15-24.
13) Vlaeyen JW, Linton SJ. Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. Pain 2000;85:317-32.
14) Abeles M, Solitar BM, Pillinger MH, Abeles AM. Update on fibromyalgia therapy. Am J Med 2006;121:555-61.
15) Kim YA, Lee SS, Park K. Validation of a Korean version of the fibromyalgia impact questionnaire. J Korean Med Sci 2002:17:
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16) Chan J, Hanekom L, Wong C, Leano R, Cho GY, Marwick TH. Differentiation of subendocardial and transmural infarction using two-dimensional strain rate imaging to assess short-axis and long-axis myocardial function. J Am Coll Cardiol 2006;48:2026-33.

17) Becker M, Hoffmann R, Kuhl HP, et al. Analysis of myocardial deformation based on ultrasonic pixel tracking to determine transmurality in chronic myocardial infarction. Eur Heart J 2006;27:2560-6.

18) Rozanski A, Blumenthal JA, Davidson KW, Saab PG, Kubzansky L. The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice: the emerging field of behavioral cardiology. J Am Coll Cardiol 2005;45:637-51.

19) Tofler GH, Muller JE. Triggering of acute cardiovascular disease and potential preventive strategies. Circulation 2006;114:1863-72.

20) Becker M, Bilke E, Kuhl H, et al. Analysis of myocardial deformation based on pixel tracking in two dimensional echocardiographic images enables quantitative assessment of regional left ventricular function. Heart 2006;92:1102-8.

21) Wittstein IS, Thiemann DR, Lima JA, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. N Engl J Med 2005;352:539-48.

22) Hong KW, Park DG, Choi HH, et al. Tako-Tsubo cardiomyopathy by transient dynamic left midventricular obstruction. Korean Circ J 2009;39:37-41.

23) Zaroff JG, Rordorf GA, Titus JS, et al. Regional myocardial perfusion after experimental subarachnoid hemorrhage. Stroke 2000;31:1136-43.

24) Vita JA, Treasure CB, Yeung AC, et al. Patients with evidence of coronary endothelial dysfunction as assessed by acetylcholine infusion demonstrate marked increase in sensitivity to constrictor effects of catecholamines. Circulation 1992;85:1390-7.

25) Mohri M, Koyanagi M, Egashira K, et al. Angina pectoris caused by coronary microvascular spasm. Lancet 1998;351:1165-9.

26) Maseri A, Crea F, Kaski JC, Crake T. Mechanisms of angina pectoris in syndrome X. J Am Coll Cardiol 1991;17:499-506.

27) Ako J, Kozaki K, Yoshizumi M, Ouchi Y. Transient left ventricular apical ballooning without coronary artery stenosis: a form of stunning-like phenomenon. J Am Coll Cardiol 2002;39:741-2.

28) Choi JO, Cho SJ, Yang IH, et al. Systolic long axis function of the left ventricle, as assessed by 2-D Strain, is reduced in the patients who have diastolic dysfunction and a normal ejection fraction. Korean Circ J 2008;38:250-6.