Left Ventricular Diastolic Dysfunction in Patients with Dermatomyositis Without Clinically Evident Cardiovascular Disease

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ABSTRACT. Objective. To assess left ventricular (LV) diastolic function in patients with dermatomyositis (DM) without clinically evident cardiovascular (CV) disease and to estimate whether there is an association between the duration of DM and LV diastolic dysfunction (LVDD).

Methods. The study included 51 patients with DM (43 women and 8 men) who had no clinically evident CV disease and 51 age-matched and sex-matched healthy controls. Echocardiographic and Doppler studies were conducted in all patients and controls. Early diastolic flow velocity/mitral annular early diastolic velocity (E/Em) was considered a marker for diastolic dysfunction.

Results. E/Em was elevated in 39 patients (76.5%) versus 27 controls (52.9%; $p < 0.05$). There were significant differences between patients versus control group in late diastolic flow velocity (A), E/A ratio, Em, Em/Am (mitral annular late diastolic velocity) ratio, E/Em ratio, and deceleration time (DT; $p < 0.05$). There was a weak correlation with disease duration between A ($r = 0.373$, $p = 0.007$), E/A ratio ($r = -0.467$, $p = 0.001$), Em ($r = -0.474$, $p < 0.001$), Em/Am ratio ($r = -0.476$, $p < 0.001$), E/Em ratio ($r = 0.320$, $p = 0.022$), and DT ($r = 0.474$, $p < 0.001$). Disease duration was associated with E/Em after controlling for age, sex, and other factors ($p < 0.05$).

Conclusion. Our study confirms a high frequency of LVDD in DM patients without evident CV disease. The association between transmitral flow alteration and disease duration may suggest a subclinical myocardial involvement with disease progression. (First Release Jan 15 2014; J Rheumatol 2014;41:495–500; doi:10.3899/jrheum.130346)

Key Indexing Terms:
DERMATOMYOSITIS   DIASTOLIC DYSFUNCTION   ECHOCARDIOGRAPHY

Dermatomyositis (DM) is an autoimmune myopathy that displays a wide range of clinical manifestations such as skin changes, interstitial lung diseases, and cardiac involvement.[1,2] Longterm survival of patients with DM is shorter compared with the general population or subjects without DM[3,4]. Cardiac involvement has been identified as the most important cause of morbidity and mortality in patients with DM[2,5,6]. The increased cardiac mortality in patients with DM has been linked to congestive heart failure. Studies have demonstrated that congestive heart failure is the most common cause of death, accounting for 21% of total cardiac mortality[2,7]. According to Lundberg[5,6], even this rate could be underestimated because of scanty epidemiological data.

Left ventricular diastolic dysfunction (LVDD) encompasses mechanical abnormalities involving decreased distensibility, impaired myocyte relaxation, and abnormal diastolic filling of the left ventricle. It has been related to old age, diabetes mellitus, metabolic syndrome, coronary artery disease, and hypertension. In the connective tissue diseases, much cardiac involvement, such as myocarditis, conduction system abnormalities, pericarditis, and myocardial infarction, has been considered responsible for LVDD[6]. In fact, these cardiac abnormalities are also among the various cardiac conditions found in DM[2]. Heart failure may result either from systolic or diastolic dysfunction or both. The importance of LVDD is that it may serve as a precursor to systolic and diastolic heart failure and may cause its own morbidity and mortality.

However, LVDD in DM is often clinically silent. Doppler echocardiography (ECG) is inexpensive, portable, and gives immediate feedback on cardiac structure, function, and flow.

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Cardiac magnetic resonance imaging (MRI) may provide detailed information on the extent of myocardial fibrosis and its morphology[8]. Several ECG studies have shown LVDD in DM. However, these studies have included a limited number of patients, lacked a control group, or enrolled patients with polymyositis (PM)[9,10,11,12]. Further, detailed investigations of LVDD in DM have yet to be performed. The importance of heart failure in DM makes it necessary to study LVDD in patients with DM.

The aim of our study was to determine LVDD in patients with DM who did not have clinically evident cardiovascular (CV) disease by Doppler ECG and to investigate whether there is a correlation between LVDD and the disease duration of DM.

MATERIALS AND METHODS

We conducted our study at the cardiology and rheumatology department of the No. 3 Hospital of Chengdu and Renming Hospital of Hubei University of Medicine, China. Fifty-one patients with an established diagnosis of DM (mean age ± SD 44.06 ± 11.80 yrs, range 18–72, 43 F) and 51 age-matched and sex-matched healthy individuals (mean age ± SD 44.41 ± 10.60 years, range 18–70, 43 F) as a control group were included in the study. The diagnosis of DM was confirmed according to the criteria of Bohan and Peter[13]. Duration of disease ranged from 0.3 to 48 months. Both patients and controls were recruited within the same time period (October 2010 to February 2013). Control subjects were referred to the hospital for diagnostic reasons and were found to be without disease after appropriate tests. Informed consent was obtained and the study was approved by the local ethics committee. None of the patients included in the study had evidence of hypertension, coronary heart disease, diabetes mellitus, cardiac arrhythmias, valvular heart disease, or chronic renal failure (as assessed by history, physical examination, and standard 12-lead ECG). None had any other connective tissue diseases, such as systemic lupus erythematosus, rheumatoid arthritis (RA), or mixed connective tissue disease. In addition, patients receiving pharmacological treatment (β-blockers, Ca channel blockers, diuretics, or other cardiac drugs) except for antirheumatic drug therapy were also excluded.

Medical history was taken and physical examinations were performed for all subjects. The lung involvement was described as pulmonary infection, pulmonary fibrosis, pulmonary tuberculosis, and interstitial lung disease according to chest computed tomography. After a 12-h fasting period, venous blood was taken in the morning from all subjects, and routine biochemical measurements were taken. The main laboratory measurements included triglyceride, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, serum uric acid, and fasting plasma glucose.

Disease activity in patients with DM was assessed by Disease Activity Score (DAS). The DAS consists of 19 items, resulting in a score of 0–20: 10 items are scored dichotomously (the indicator is present or not), and 3 polychotomously (rating severity levels or extent to which the indicator is present)[14]. The DAS has been used widely, and exhibits evidence of good reliability and validity[14].

ECG was performed on a GE Vingmed System 5 performance machine and 2.5-MHz electronic transducer. All patients were examined in the left parasternal and apical windows with normal breathing. M-mode and 2-dimensional (2-D) ECG were performed, followed by Doppler. The cardiac chamber dimension and wall thickness were obtained from M-mode and 2-D ECG. LV ejection fraction was calculated according to Simpson's formula. Pulsed-wave tissue Doppler was performed in both patients and controls, with a frame rate of about 70. Using tissue Doppler imaging program, a 5-mm sample volume was placed at the medial corner of the mitral annulus in the 4-chamber view.

The following M-mode and 2-D measurements were assessed: LV diameter, left atrial diameter, interventricular septum thickness, LV posterior wall thickness, LV end-diastolic dimension, LV end-systolic dimension, LV end-diastolic volume, and LV end-systolic volume.

The following Doppler measurements were assessed as variables of the LV diastolic function: mitral peak of early diastolic (E) and late diastolic (A) flow velocity, E/A ratio, mitral annular early diastolic (Em) and late diastolic (Am) velocity (performed by tissue Doppler), Em/Am ratios, E/Em ratios, deceleration time of flow velocity in early diastole (DT) and isovolumic relaxation time (IVRT). Doppler measurements were averaged more than 5–10 cardiac cycles. E/Em ratio, the most commonly used measure reflecting LVDD, was calculated. Possible diastolic dysfunction was defined as E/Em > 8.

Statistical analysis was performed using SPSS 16.0 for Windows (SPSS). Data are presented as mean ± SD, median (range 25th–75th percentile), and percentage. Continuous data that are normally distributed were analyzed by paired Student's t-test; where not normally distributed, variables are analyzed using Mann-Whitney U test. Discrete data are compared with chi-square test. Correlation between variables is performed using Spearman's rank correlation. The association between E/Em and disease duration was controlled for age, sex, and other factors in linear regression models. P values < 0.05 were considered significant.

RESULTS

The characteristics of patients included in the study are summarized in Table 1. There were no significant differences between groups regarding the age, sex, systolic and diastolic blood pressures, heart rate, serum uric acid, and fasting plasma glucose. There was a significant difference between the groups regarding the level of triglyceride, while total cholesterol, HDL cholesterol, and LDL cholesterol levels did not differ significantly among the patients in either group. Duration of disease and the DAS in patients with DM ranged from 0.3 to 48 months, and 5 to 17, respectively. In addition, the use frequency of glucocorticoid, methotrexate, azathioprine, cyclophosphamide, hydroxychloroquine, intravenous immunoglobulin, and biologics, were 94.11%, 25.49%, 3.92%, 21.57%, 58.82, 0%, and 0%, respectively.

ECG and Doppler variables in patients with DM were compared with those of healthy individuals (Table 2). E/A ratio, Em, and Em/Am ratio were significantly lower in patients with DM than in healthy individuals ($0.97 ± 0.33$ vs $1.20 ± 0.28$, p < 0.001; $7.78 ± 2.90$ cm/s vs $9.32 ± 2.10$ cm/s, p < 0.05; 0.89 (0.64, 1.22) vs 1.18 (1.04, 1.29), p < 0.01, respectively). A, E/Em, and DT were found to be higher in patients with DM than in the control group ($0.77 ± 0.18$ m/s vs $0.67 ± 0.13$ m/s, p < 0.05; $9.92 ± 2.82$ vs $8.67 ± 1.92$, p < 0.05; $231.75 ± 40.60$ m/s vs $208.20 ± 26.30$ m/s, p < 0.01, respectively). There were no significant differences for E, Am, and IVRT between the patients and the healthy individuals (p > 0.05). In addition, there were no differences between the 2 groups regarding LV dimensions, interventricular septum thickness, posterior wall thickness, aortic root diameter, ascending aorta diameter, main pulmonary artery diameter, LV end-diastolic dimension, LV end-systolic dimension, LV end-diastolic volume, or LV end-systolic volume (p > 0.05). Of note, patients with DM

Table 1. Clinical features of patients with dermatomyositis and controls. Data are mean ± SD unless otherwise indicated.

Clinical Features	Patients, n = 51	Controls, n = 51
Age, yrs	44.06 ± 11.80	44.41 ± 10.60
Female, %	84.31	84.31
Duration, mos (range)	8 (0.3, 48)	—
DAS score (range)	10 (5, 17)	—
Muscle weakness, %	100	—
Myalgia, %	28.41	—
Polyarthralgia, %	35.29	—
Heliotrope rash, %	64.71	—
Gottron sign, %	60.78	—
Shawl sign, %	17.65	—
Raynaud phenomenon, %	7.84	—
Lung involvement, %	52.94	0
Systolic BP, mmHg	117.61 ± 11.57	118.67 ± 10.03
Diastolic BP, mmHg	72.14 ± 12.93	74.76 ± 7.27
Heart rate, beats/min	81.35 ± 6.74	80.10 ± 4.13
Triglyceride, mmol/l	1.68 ± 0.77	1.36 ± 0.79*
Total cholesterol, mmol/l	4.79 ± 1.23	4.77 ± 0.70
LDL cholesterol, mmol/l	2.85 ± 1.21	2.71 ± 0.66
HDL cholesterol, mmol/l	1.44 ± 0.45	1.54 ± 0.34
Serum uric acid, umol/l	306.49 ± 95.38	330.20 ± 93.52
Fasting plasma glucose, mmol/l	4.78 ± 0.79	4.84 ± 0.67
ANA-positive, %	84.31	0
Anti-Jo1 antibody-positive, %	9.80	0
Medications, %		
Glucocorticoid	94.11	0
Methotrexate	25.49	0
Azathioprine	3.92	0
Cyclophosphamide	21.57	0
Hydroxychloroquine	58.82	0
IVIG	0	0
Biologics	0	0

p < 0.05. DAS: Disease Activity Score; BP: blood pressure; LDL: low-density lipoprotein; HDL: high-density lipoprotein; IVIG: intravenous immunoglobulin; ANA: antinuclear antibody.

had similar LV systolic function such as LV stroke volume (p = 0.069), LV ejection fraction (p = 0.120), and LV fractional shortening (p = 0.284) compared with those of healthy individuals.

Correlations between LV diastolic function measures and disease duration/disease activity in patients with DM are shown in Table 3. Spearman's rank correlation demonstrated that the duration of DM correlated negatively with E/A ratio, Em, and Em/Am ratio (r = –0.467, p = 0.001; r = –0.474, p < 0.001; r = –0.476, p < 0.001, respectively), and positively with A, E/Em, and DT (r = 0.373, p = 0.007; r = 0.320, p = 0.022; r = 0.474, p < 0.001, respectively). However, the DAS did not correlate with ECG measures (p > 0.05).

We assessed the association between E/Em ratio and disease duration in a linear regression model (Table 4). After adjustment for age and sex, linear regression demonstrated that disease duration is associated with E/Em ratio among patients with DM (p = 0.029). After controlling for age, sex, DAS, heart rate, fasting plasma glucose, and blood pressure, disease duration was still associated with E/Em ratio in a linear regression model (p = 0.014).

DISCUSSION

Our present study confirms a high frequency of LVDD in patients with DM without evident CV disease compared with control subjects matched for age and sex. Significant differences between groups in values of A, E/A ratio, Em, Em/Am ratio, E/Em ratio, and DT estimated by Doppler echocardiography were observed. In addition, we also found a weak correlation between these transmitral flow alterations and DM duration. These findings suggest a subclinical myocardial involvement with disease progression, which may partly account for the high incidence of CV deaths observed in patients with DM.

Previous studies reported that LVDD represented a high frequency rate of cardiac involvement in adult DM[2]. However, to the best of our knowledge, LVDD was only reported in 4 case series, and subjects in these studies included patients with PM[8,9,10,11]. Gupta, *et al* performed a systematic review, and found that LVDD was the most common ECG finding, occurring in 34.5% (30/87) of DM/PM cases[2]. Other authors found impaired diastolic function in juvenile DM[15]. These findings are in accordance with our results. Analogous to the studies in DM, LVDD is also a striking feature of other autoimmune disorders, including RA. For example, changes of E, E/A ratio, Em, Em/Am ratio, and DT were reported in line with those of systemic sclerosis (SSc) and RA[16,17].

However, the underlying mechanisms of LVDD in DM remain unclear. Limited evidence from myocardial biopsies has demonstrated that several mechanisms may be responsible for diastolic dysfunction in DM. Myocarditis is thought to be one of the most important pathological changes during DM course[2]. A study by Lie revealed myocarditis in about 30% of patients with DM who did not have clinical cardiac symptoms[18]. Autopsy studies have also confirmed that the histopathology of myocarditis resembles the inflammation in the skeletal muscle, with mononuclear inflammatory cell infiltrates localized to the endomysium and to the perivascular areas[6]. The myocardial inflammatory process would lead to the degeneration of myocytes and evolution to tissue fibrosis. Primary myocarditis and impaired relaxation in DM may be the result of fibrotic lesions[2,6]. Myocardial fibrosis is a frequent pathological change, which often coexists with myocarditis in the same patients, indicating that myocardial damage may be explained by a combination of acute inflammatory infiltrates and chronic fibrosis[19]. Recent studies have demonstrated that cardiac MRI is helpful in the diagnosis of acute inflammatory myocarditis and myocardial fibrosis[20]. Allanore, *et al*[21] found that cardiac MRI had a higher sensitivity to detect myocardial inflammatory areas compatible

Table 2. Echocardiographic and Doppler variables in patients with dermatomyositis and controls. Data are mean ± SD unless otherwise indicated.

Variable	Patients, n = 51	Controls, n = 51	p
Left ventricular (LV) diameter, mm	44.57 ± 4.36	45.24 ± 3.22	NS
Left atrium diameter, mm	30.39 ± 3.72	29.51 ± 2.80	NS
Interventricular septum thickness, mm (range)	9 (8, 10)	9 (8, 10)	NS
Posterior wall thickness, mm (range)	9 (8, 10)	9 (8, 9)	NS
Aortic root diameter, mm (range)	28 (26, 29)	27 (26, 28)	NS
Ascending aorta diameter, mm (range)	28 (27, 31)	27 (26, 28)	NS
Main pulmonary artery diameter, mm (range)	20 (19, 22)	18 (17, 20)	NS
LV end-diastolic dimension, mm (range)	45 (43, 47)	45 (43, 48)	NS
LV end-systolic dimension, mm (range)	28 (26, 30)	28 (27, 30)	NS
LV end-diastolic volume, ml (range)	92 (83, 104)	93 (83, 106)	NS
LV end-systolic volume, ml	30 (25, 34)	30 (26, 35)	NS
Peak of early diastolic flow velocity (E), m/s	0.72 ± 0.19	0.79 ± 0.16	NS
Peak of late diastolic flow velocity (A), m/s	0.77 ± 0.18	0.67 ± 0.13	< 0.05
E/A ratio	0.97 ± 0.33	1.20 ± 0.28	< 0.001
Mitral annular early diastolic velocity (Em), cm/s	7.78 ± 2.90	9.32 ± 2.10	< 0.05
Mitral annular late diastolic velocity (Am), cm/s (range)	8 (7, 9)	7.3 (6.8, 9.2)	NS
Em/Am ratio (range)	0.89 (0.64, 1.22)	1.18 (1.04, 1.29)	< 0.01
E/Em ratio	9.92 ± 2.82	8.67 ± 1.92	< 0.05
Deceleration time of flow velocity in early diastole (DT), ms	231.75 ± 40.60	208.20 ± 26.30	< 0.01
Isovolumic relaxation time, ms	81.06 ± 19.31	77.41 ± 11.32	NS
LV stroke volume, ml	61.16 ± 12.21	65.35 ± 10.83	0.069
LV ejection fraction, %	66.45 ± 6.81	68.20 ± 4.11	0.120
LV fractional shortening, % (range)	38 (34, 40)	38 (36, 41)	0.284

NS: not significant ($p > 0.05$).

Table 3. Correlation of left ventricular diastolic function variables and duration/DAS score in patients with dermatomyositis (DM).

Variables	DM Duration		DAS	
	r	p	r	p
Peak of early diastolic flow velocity (E)	−0.247	0.080	−0.180	0.206
Peak of late diastolic flow velocity (A)	0.373	0.007	0.003	0.981
E/A ratio	−0.467	0.001	−0.229	0.106
Mitral annular early diastolic velocity (Em)	−0.474	< 0.001	−0.122	0.395
Mitral annular late diastolic velocity (Am)	0.045	0.756	0.111	0.437
Em/Am ratio	−0.476	< 0.001	−0.208	0.143
E/Em	0.320	0.022	0.009	0.950
DT of flow velocity in early diastole	0.474	< 0.001	0.213	0.133
Isovolumic relaxation time	0.261	0.065	0.222	0.117

DAS: Disease Activity Score; DT: deceleration time.

with myocarditis in 3 cases with inflammatory myopathies than did conventional laboratory tests such as ECG. However, there was no confirmation on cardiac MRI of our imaging data, because this procedure was judged to be too expensive and time-consuming to be incorporated into our study. In addition, vascular alterations, such as vasculitis, intima hyperplasia, and tunica media sclerosis of the heart with vasospasm angina have been reported in coronary arteries[22,23,24], so coronary atherosclerosis may be common in patients with DM. These findings suggest that vascular alterations in coronary atherosclerosis may involve the pathogenesis of myocardial dysfunction. In our present study, we included patients with DM who did not have clinically evident CV disease, and those patients did not receive β-blockers, Ca channel blockers, diuretics, or other cardiac drugs except for antirheumatic drug therapy. In addition, the progressive impairment of diastolic function with age is well known[25], but the ages of patients with DM were matched with controls, and no significant difference was found between the groups regarding age. Many antirheumatic drugs, such as gold salts, chloroquine, D-penicillin, and hydroxychloroquine have cardiotoxic side effects, and could cause myocardial function abnormalities[26]. However, our patients did not receive these drugs. It

Table 4. The association between E/Em and disease duration in linear regression models.

	B	SE	β	t	p
Model 1					
Constant	6.922	1.551	—	4.464	0.000
Age	0.046	0.034	0.193	1.345	0.185
Sex	0.448	1.071	0.058	0.418	0.678
Disease duration	0.091	0.041	0.318	2.246	0.029
Model 2					
Constant	15.5	6.870	—	2.256	0.029
Age	0.055	0.037	0.231	1.489	0.144
Sex	0.885	1.133	0.115	0.782	0.439
Disease duration	0.131	0.051	0.457	2.575	0.014
DAS	0.041	0.146	0.042	0.280	0.780
Heart rate	−0.113	0.063	−0.270	−1.798	0.079
Fasting plasma glucose	−0.358	0.544	−0.100	−0.658	0.514
Systolic BP	0.003	0.046	0.011	0.057	0.955
Diastolic BP	0.010	0.044	0.046	0.225	0.823

E/Em: early diastolic flow velocity/mitral annular early diastolic velocity; DAS: Disease Activity Score; BP: blood pressure; B: regression coefficient; SE: standard error.

has been demonstrated that treatment with intravenous methylprednisolone followed by prednisone and immunosuppressive therapy seems to be effective for treating myocardial involvement in patients with PM[21]. Additionally, treatment with biologics was found to be associated with lower LV mass and smaller LV volumes in patients with RA[27]. However, whether corticosteroids, immunosuppressors, and biologics result in diastolic dysfunction remains unknown, although these studies showed a relationship between these medications and cardiac structure/tissue. Therefore, the diastolic function abnormalities that we found, in the absence of systolic abnormalities, could suggest an intrinsic myocardial involvement.

In our present study, we found a statistically significant association between transmitral flow alteration and duration of DM, consistent with previous studies in RA and SSc, which may suggest a subclinical myocardial involvement with disease progression. In fact, "long" duration often is associated with continuing cell damage, pathological calcification, and high level of cytokines such as vascular cell adhesion molecule 1 and tumor necrosis factor-α, compared with "short" duration in patients with juvenile DM, who did not receive cardiac drugs[28,29,30]. Therefore, long disease duration may lead to LVDD because these factors influence diastolic function in DM. These observations may offer benefits in controlling the disease progression and routine examination by Doppler in DM. Similar to previous studies focusing on RA[31,32], there was no statistically significant correlation between ECG measurements in our patients and values of DAS. However, some authors found impaired systolic function assessed by relative long-axis shortening of the left ventricle (long-axis strain) in juvenile DM[33]. The difference in evaluation methods may explain the results. Medications may be involved in the process as a result of the therapeutic effect of antiinflammatory agents.

Our current study has some limitations. First, the sample of patients was relatively small. However, to our knowledge, this is the largest clinical trial focusing on cardiac function in the rare disease. Additionally, because differences between patients and controls for the outcome measures were generally large with limited variability, even small differences were detectable within the bounds of statistical significance. Second, the main limitation of ECG assessing cardiac function is that it is not specific for myocardial fibrosis, and the ECG variables are influenced by the patient's heart rate, blood pressure, body mass index, and ECG window view. Compared with ECG, cardiac MRI appears to provide additional information by visualizing myocardial fibrosis and inflammation because of its superiority in resolution, sensitivity, and reproducibility. In fact, the cardiac manifestations in DM are silent, often leading to delayed diagnosis, and cardiac evaluation with cardiovascular MRI is sensitive enough to detect these abnormal findings in patients with autoimmune diseases missed by conventional ECG[34]. Third, we did not provide the detailed mechanism on LVDD owing to the absence of endomyocardial biopsies, which have been used to confirm myocardial inflammation in patients with DM; however, this invasive method has rarely been used in clinical practices. Lastly, clinical followup by ECG will also provide us with detailed data on cardiac function in patients with DM.

LVDD may be a common feature in patients with DM without evident CV disease. Significant correlation between the degree of LVDD and duration of DM was also observed. These results revealed a subclinical myocardial involvement with disease progression. Therefore, it is reasonable to suggest that these patients should be routinely evaluated for LV diastolic function to minimize the longterm risk of CV disease even in the early stages of disease, when cardiac

involvement is clinically silent. More research is needed to quantify the underlying mechanisms of LVDD in DM.

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