Subclinical Cardiac Dysfunction in Polymyositis and Dermatomyositis: A Speckle-tracking Case-control Study

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ABSTRACT. ***Objective.*** Subclinical heart disease occurs in up to 50% of patients with idiopathic inflammatory myopathies (IIM) and is difficult to detect through conventional imaging. We investigated the usefulness of global longitudinal strain (GLS) measurement to detect a subclinical systolic ventricular dysfunction in patients with IIM.

Methods. We enrolled 28 patients with IIM and 28 matched controls in a 1:1 fashion. Standard variables for the left ventricle (LV) and right ventricle (RV) systolic and diastolic function were measured and compared between cases and controls, along with speckle-tracking GLS of the LV and RV. A possible correlation between GLS and muscle strength, disease activity, cardiovascular risk factors, and other organ systems involvement was searched.

Results. Standard variables of systolic and diastolic dysfunction were similar between patients and controls. GLS was significantly lower in patients when compared with controls for both LV (–18.7 ± 4.2% vs –21.2 ± 2.1%, p = 0.006) and RV (–19.3 ± 6.3% vs –22.5 ± 3.8%, p = 0.033). Patients with IIM had a 4.9-fold increased risk for impaired left GLS [relative risk (RR) 4.9, 95% CI 1.5–15.8, p = 0.006], which involved usually basal and mid-segments of the anterior, anterior-septal, and lateral wall. Patients with IIM had a 3.4-fold increased risk for impaired right GLS (RR 3.4, 95% CI 1.1–11.7, p = 0.04) with the basal segment of the free RV wall most frequently involved. Muscle strength, disease activity, damage and duration, other organ system involvement, and previous treatment were not associated with reduced GLS.

Conclusion. Subclinical systolic impairment is common in patients with IIM without overt LV dysfunction. In this context, GLS is a potentially useful variable. (First Release April 1 2017; J Rheumatol 2017;44:815–21; doi:10.3899/jrheum.161311)

Key Indexing Terms:
DERMATOMYOSITIS ECHOCARDIOGRAPHY POLYMYOSITIS
SPECKLE ECHOCARDIOGRAPHY SYSTOLIC STRAIN

Idiopathic inflammatory myopathies (IIM) are systemic immune-mediated diseases that involve the skeletal muscle and several other organ systems, such as the lung, the gastrointestinal tract, the skin, and the heart[1]. Cardiac involvement became more relevant in recent years and this is primarily related to the development of new diagnostic techniques and to the effect that cardiac disease has on IIM prognosis[2,3,4,5,6]. However, the heterogeneity of clinical presentation, the different inclusion and exclusion criteria, the lack of agreement on definition of heart involvement, and the different methods used to detect cardiac abnormalities still influence the interpretation of data available in literature[7,8,9].

Usually, cardiac assessment in patients with IIM is performed using clinical, laboratory, and radiologic data[10,11,12,13,14,15]. High-sensitivity troponin I (hsTnI) is currently the laboratory gold standard to assess myocardial injury, being minimally influenced by skeletal muscle activity[16], while ultrasound (US) imaging represents the less invasive and more used technique to identify structural cardiac alterations, reserving magnetic resonance imaging and stress/rest scintigraphy only for selected cases[3,4,5,6]. The alterations that can affect cardiac function are mainly due to the impairment of ventricular filling (diastolic function) and of cardiac output (systolic function). Currently, systolic

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function is usually assessed by the measurement of left ventricle (LV) ejection fraction (LVEF) and by the tricuspidal annulus plane systolic excursion (TAPSE) for the right ventricle (RV). The comparative analysis of pulse-wave Doppler analysis at mitral and tricuspidal level and the tissue Doppler imaging (TDI) at the level of the mitral annulus provide a reliable estimate of ventricular diastolic function[17].

Several studies reported a compromised left ventricular diastolic dysfunction (LVDD), assessed by TDI, in patients with myositis[11,12,13,14,15]. However, the evaluation of systolic function and heart contractility remains strictly related to the measurement of LVEF that usually worsens only when heart function is severely affected[17]. In our study, we used speckle-tracking echocardiography (STE) with the measurement of the cardiac global longitudinal strain (GLS) as a noninvasive method to assess myocardial deformation and subclinical involvement[18]. This technique has already been validated as a critical marker in assessing subclinical heart involvement in specific settings, such as in patients with cancer undergoing different types of antineoplastic therapies or specific subpopulations[19,20,21] and is associated with an increased risk of developing cardiac sequelae such as heart failure, ischemic heart disease, and cardiogenic shock[22].

The aim of our study was to investigate the presence of subclinical heart involvement in patients with polymyositis (PM) and dermatomyositis (DM) by using the STE and GLS measurement of the RV and LV. We also studied, as secondary objectives, a possible correlation between GLS and type of myositis, disease activity and duration, and presence of conventional cardiovascular (CV) risk factors [such as diabetes, hypertension (HTN), dyslipidemia, obesity, and smoking].

MATERIALS AND METHODS

Study population. We enrolled all consecutive patients referred to the Clinica Medica, Dipartimento di Scienze Cliniche e Molecolari, a tertiary referral center for myositis management in central Italy, from April 2015 to June 2016. The diagnosis of definite idiopathic PM or idiopathic DM was made according to the Bohan and Peter criteria and confirmed by muscle biopsy[23]. Patients with inclusion body myositis, necrotizing autoimmune myositis, overlap myositis, and juvenile myositis were excluded from our study. Myositis cases were matched in a 1:1 fashion with controls admitted in our out-of-hospital Cardiology Clinic as part of clinical assessment in patients undergoing noncardiac surgery. All controls were asymptomatic at baseline and showed no previous cardiac history.

Case-control matching was performed in the following way: for each patient with IIM enrolled, all subsequent outpatients without underlying heart disease were screened until a patient of the same sex in the same decade of age and the same CV risk factors was found. Patients and controls with preexisting known structural heart disease, coronary heart disease, moderate to severe valve disease, valve replacement, heart failure with reduced or preserved ejection fraction, sleep apnea, pulmonary disease (including prior deep vein thrombosis/pulmonary embolism), and pulmonary HTN were excluded. Patients and controls with atrial fibrillation at the time of enrollment were also excluded because of the inability to perform accurate STE measurements.

The study was conducted according to the Declaration of Helsinki. A formal Ethics Committee approval was not required in accordance with the policy of our institution; the work conforms to standards currently applied in Europe. All patients gave their informed consent before entering the study.

Data collection. All patients' data were collected by means of a standardized protocol including demographics and clinical and functional characteristics (performed by MGD and CG). Cardiologic clinical history collection and physical examination of all patients and controls were performed by a single physician (FG). The muscle evaluation was based on the modified Medical Research Council (mMRC) scale, which assesses changes in skeletal muscle strength in 10 muscular districts using a quantitative score in which 0 is the lowest score and 11 the highest for each segment assessed (performed by CG). During the visit, blood samples were drawn to obtain complete blood count and renal and liver function. Serum creatine kinase (CK; normal values < 170 U/l) and hsTnI (normal values < 0.055 ng/ml) levels were selected as biochemical indices of muscle damage. In the presence of a myopathic pattern at the electromyographic examination, the diagnosis was confirmed by muscle biopsy specimens analyzed using light and electron microscopy. Disease activity and damage were defined according to specific indices assessed by trained physicians: the Myositis Intention to Treat Activities Index (MITAX) for global disease activity and the Myositis Damage Index (MDI) extent score for damage[24,25]. Clinical remission was defined as an increase in strength of at least 1 more mMRC point in at least 3 affected muscles with normal CK levels.

Data related to treatment [glucocorticoids, immunosuppressive agents, and intravenous (IV)/subcutaneous (SC) immunoglobulin (Ig)] were collected with related side effects or complications.

Cardiac imaging. Echocardiographic examinations were performed with monoplane US probe 4 MHz (M4S) of Vivid 7 Pro (GE Medical Systems) by a single trained cardiologist (FG) who was blinded to the clinical characteristics of the patients. Images were identified digitally, recording at least 3 consecutive beats, and analyzed offline using dedicated software (EchoPAC 13.0; GE Medical Systems) by the same single operator who ultimately derived echocardiographic standard measurements and 2-dimensional STE myocardial deformation variables according to the most recent recommendations[17]. The echocardiographic images were obtained with the patient supine and in left lateral decubitus at the end of a normal breath, minimizing the depth to optimize the frame rate (40–80 fps). LVEF was calculated by the Simpson biplane method, obtaining a minimum of 3 complete sets of measurements, from which the average values were calculated. Right ventricular systolic function was also assessed by M-mode TAPSE and by right ventricular fractional area change (FAC). Diastolic dysfunction was assessed by pulse-wave Doppler analysis at mitral and tricuspidal level, to obtain early (E) and late (A) diastolic filling velocities and to calculate the E/A and E/E ratios. TDI was performed on mitral and tricuspidal annuli to collect lateral and septal E waves and tricuspidal S wave. STE was used to assess GLS of the LV and RV. We excluded the interventricular septum from RV GLS calculations because it was recently reported to have prognostic value in various disease states, such as heart failure and acute coronary syndrome[17,26,27]. While no consensus has been reached regarding a specific cutoff value of GLS for systolic dysfunction, current guidelines suggest that a value higher than –20% (i.e., < 20% in absolute value) is likely abnormal for both LV and RV[17].

Image quality was ensured to permit complete software analysis of all cardiac segments. If the software rejected some segments for poor image quality, another single attempt was performed to improve manual endocardial tracking, and if unsuccessful, the segment still considered inadequate was excluded from the analysis. The aortic valve closure was automatically selected by the software through electrocardiogram gating to obtain measures as reproducible as possible. No more than 1 segment out of the total 20 (17 LV segments and 3 RV segments) was considered inadequate by the software in every single examination.

Statistical analysis. Quantitative variables were checked for normality by the Kolmogorov-Smirnov test. Normally distributed variables were described as mean ± SD. Not-normally distributed variables were described as median and interquartile range (IQR). ANOVA was used to compare normally distributed quantitative variables. Kruskal-Wallis ANOVA was

used to compare non-normally distributed quantitative variables. Categorical variables were assessed using the chi-square analysis, and described as absolute or relative prevalence. SPSS 18.0 for Windows (SPSS Inc.) was used for statistical analysis. Values of $p < 0.05$ (2-tailed) were considered statistically significant.

RESULTS

General characteristics. Twenty-eight patients with IIM and 28 matched controls were enrolled in our study. Their baseline characteristics are shown in Table 1. Mean age of patients with IIM was 61.3 ± 13.1 years, and 22 (78.6%) were women. Median time from diagnosis of myositis to enrollment was 44 months (IQR 3–65 mos). Six patients (21%) presented no active skeletal muscle activity at the time of our study. No patient reported cardiac-related symptoms. Plasma levels of hsTnI were significantly higher in patients when compared with controls (p = 0.02; Table 1).

Left and right ventricular function. Table 2 reports the data related to the left and right ventricular systolic and diastolic functions. We found no significant differences between patients with IIM and controls regarding standard indices of left ventricular systolic and diastolic function. According to E/A ratios, 21 patients and 15 controls were classified with a mild LVDD (grade I, 75.0% vs 53.6%, p = not significant). Similarly, RV systolic and diastolic variables were not significantly different in patients and controls. In particular, right E/A ratio was similar in the 2 groups (1.1 ± 0.4 vs 0.9 ± 0.4, p = not significant), with 17 patients and 10 controls classified as having mild (grade I) right ventricular diastolic dysfunction (60.7% vs 35.7%, p = not significant).

Speckle-tracking GLS. LV GLS was significantly lower in patients when compared with controls (–18.7 ± 4.2% vs –21.2 ± 2.1%, p = 0.006; Figure 1). Using –20% as a cutoff value[17], 6 controls (21.4%) had an impaired GLS compared with 16 patients with IIM (57.1%). Patients with IIM had a 5-fold increased risk for impaired left GLS [relative risk (RR) 4.9, 95% CI 1.5–15.8, p = 0.006]. LV GLS in patients with IIM was lower in basal and mid-segments of the anterior, anterior-septal, and lateral wall.

Also, RV GLS was significantly lower in patients when compared with controls (–19.3 ± 6.3% vs –22.5 ± 3.8%, p = 0.033; Figure 1). Using the same cutoff value (–20%)[17], 5 controls (17.8%) had an impaired right GLS compared with 12 patients with IIM (42.9%), resulting in a 3-fold increased risk for impaired right GLS (RR 3.4, 95% CI 1.1–11.7, p = 0.04). The basal segment of the free right ventricular wall was the segment with lower GLS in patients with IIM (Figure 2).

Table 1. General characteristics of patients with IIM and controls. Values are n (%) unless otherwise specified.

Characteristic	IIM, n =28	Controls, n = 28	p
Age, yrs, mean ± SD	61.3 ± 13.1	63.6 ± 15.6	0.53
Female	22 (78.6)	22 (78.6)	1
Smoking habit	2 (7.1)	4 (14.3)	0.75
Hypertension	12 (60.0)	12 (60.0)	1
Diabetes mellitus	2 (7.1)	2 (7.1)	1
Dyslipidemia	4 (14.3)	4 (14.3)	1
BMI, kg/m^2, mean ± SD	26.4 ± 4.2	25.2 ± 4.4	0.344
Troponin I, ng/ml, mean ± SD	0.07 ± 0.03	0.03 ± 0.02	0.020
Serum CK levels, U/l, median (range)	257 (100–602)	23 (12–104)	< 0.001
ACE inhibitors	2 (7.1)	2 (7.1)	1
Sartans	1 (3.6)	2 (7.1)	0.348
β blockers	5 (17.8)	6 (21.4)	0.713
Calcium channel blockers	2 (7.1)	1 (3.6)	0.348
Oral hypoglycemic agents	1 (3.6)	1 (3.6)	1
Insulin	0 (0)	1 (3.6)	1
Time to myositis diagnosis, mos, median (range)	44 (3–65)	—	—
mMRC, mean ± SD	78.9 ± 8.2	—	—
MITAX, mean ± SD	0.16 ± 0.12	—	—
MDI, mean ± SD	0.11 ± 0.06	—	—
Immunoglobulin therapy			
Intravenously	20 (71.4)	—	—
Subcutaneously	18 (64.2)	—	—
Glucocorticoids	25 (89.3)	—	—
Methotrexate, 0.15–0.2 mg/kg/week orally	5 (17.9)	—	—
Cyclosporine, 3 mg/kg/day orally	2 (7.1)	—	—
Hydroxychloroquine, 3–5 mg/kg/day orally	5 (17.9)	—	—
Azathioprine, 1.5 mg/kg/day orally	1 (3.6)	—	—
Mycophenolate, 30 mg/kg/day orally	1 (3.6)	—	—

IIM: idiopathic inflammatory myopathies; BMI: body mass index; CK: creatine kinase; ACE: angiotensin-converting enzyme; mMRC: modified Medical Research Council; MITAX: Myositis Intention to Treat Activities Index; MDI: Myositis Damage Index.

Table 2. Results of ultrasound assessment of left and right ventricular systolic and diastolic function in patients with idiopathic inflammatory myopathies and controls. Values are mean ± SD unless otherwise specified.

Variable	Patients, n = 28	Controls, n = 28	p*
Assessment of the systolic function			
Left ventricle			
LVEF, %	65.9 ± 6.7	63.4 ± 4.8	NS
E', lateral, m/s	0.12 ± 0.4	0.11 ± 0.4	NS
E', septal, m/s	0.09 ± 0.3	0.09 ± 0.2	NS
GLS, %	–18.7 ± 4.2	–21.2 ± 2.1	0.006
Right ventricle			
TAPSE, mm	21.6 ± 3.8	23.4 ± 3.9	NS
FAC, %	40.2 ± 4.4	41.8 ± 4.6	NS
S', m/s	0.11 ± 0.02	0.12 ± 0.04	NS
GLS, %	–19.3 ± 6.3	–22.5 ± 3.8	0.033
Assessment of the diastolic function			
Left ventricle			
E/A, m/s	1.0 ± 0.7	1.0 ± 0.6	NS
E/E', m/s	6.9 ± 3.3	8.0 ± 3.8	NS
Right ventricle			
E/A, m/s	1.1 ± 0.4	0.9 ± 0.4	NS

* Significance set at $p < 0.05$. LVEF: left ventricle ejection fraction; E: early diastolic filling velocity; E': early diastolic filling wave on tissue Doppler imaging; GLS: global longitudinal strain; TAPSE: tricuspidal annulus plane systolic excursion; FAC: fractional area change; S': peak systolic annular velocity on tissue Doppler imaging; A: late diastolic filling velocity; NS: not significant.

Comparison between disease activity/damage and GLS score. According to univariate analysis, these were not associated with a significant difference in left or right GLS in patients with IIM: disease duration, current illness activity, muscle strength (mMRC), disease activity (MITAX) and damage (MDI), serum level of hsTnI, previous therapy with cardiotoxic agents, or current therapy with glucocorticoid or Ig. Diagnosis of concomitant esophageal, cutaneous, or pulmonary involvement was not associated with a reduced GLS (Figure 3).

DISCUSSION

Heart involvement is becoming a major cause of death in patients with myositis[2,5,6]. In our series of 91 patients with IIM, cardiac involvement increased the risk of mortality of about 2× (HR 1.8), and this association was also confirmed in the multivariate model[28]. Data reported that subclinical heart involvement, characterized by biochemical and instrumental modifications, is estimated to affect around 70% of patients with myositis[2,5]. In our study, we used STE, a non-invasive method, to assess GLS, a new variable that evaluates myocardial deformation. We observed that subclinical systolic dysfunction of both LV and RV is more prevalent in myositis than previously thought (even in patients considered to be in remission) and occurred in around half of patients. To our knowledge, there are no studies in the literature of adult patients with myositis using the GLS to assess the left or right ventricular systolic dysfunction, but there are reports about juvenile DM demonstrating worse strain measurements compared with healthy controls[29].

Using –20% as effective in ruling out subclinical damage in our population, patients with IIM had a 4.9-fold increased risk of a left systolic dysfunction when compared with controls. It is important to note that impaired left ventricular systolic function detected by GLS occurs even in patients having a preserved LVEF, implying that GLS assessment is a precocious marker of heart involvement and a potentially treatable feature. Nowadays, the impairment of LVEF is

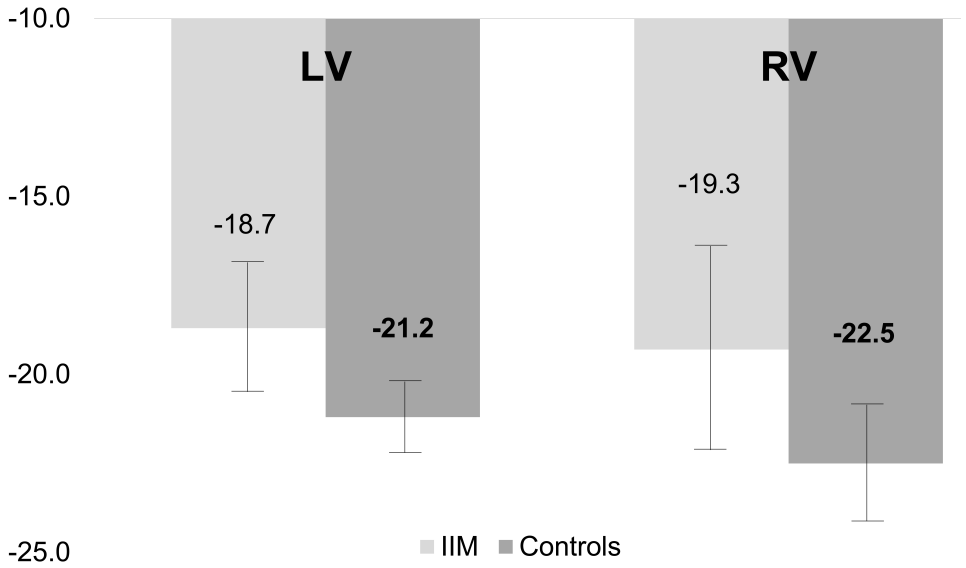

Figure 1. Global longitudinal strain in LV and RV in patients with IIM and in controls. LV: left ventricle; RV: right ventricle; IMM: inflammatory myopathies.

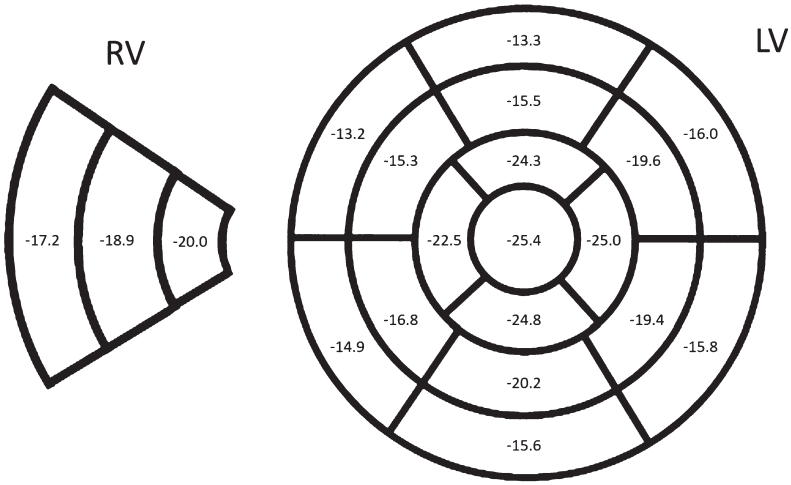

Figure 2. Mean global longitudinal strain score of patients with myositis for each ventricular wall segment. LV: left ventricle; RV: right ventricle.

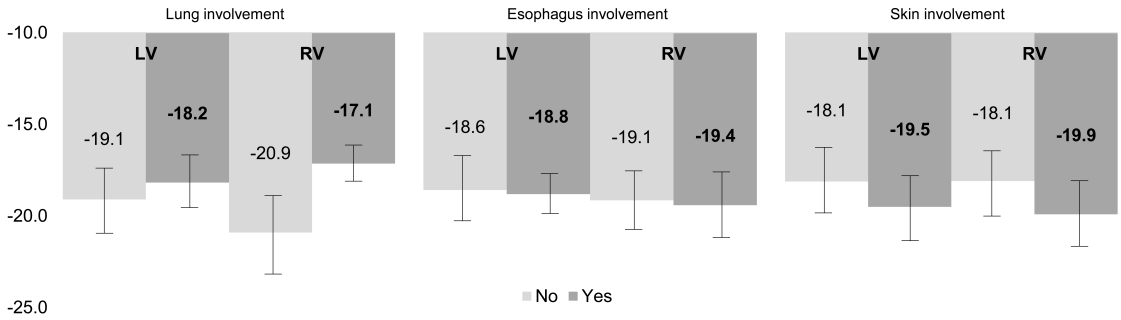

Figure 3. Organ involvement and global longitudinal strain. Global longitudinal strain in LV and RV in patients with inflammatory myopathies according to the presence (Yes) or the absence (No) of the involvement of a specific organ: lung, esophagus, and skin. LV: left ventricle; RV: right ventricle.

considered by some authors a late marker of cardiac damage[17]. It is thus possible that standard echocardiographic variables of systolic dysfunction are somewhat inadequate in detecting subclinical heart involvement. Péter, *et al*[15] reported an LV dysfunction at the onset of the disease in 30 hospitalized patients with PM/DM without clinical cardiac symptoms by using the TDI analysis instead of the LVEF assessment. In this regard, GLS may be less user-dependent and more reliable compared to biplane LVEF calculation and TDI because it is not angle-dependent and is automatically quantified by the software[17].

Concerning left ventricular diastolic function, there are several studies that documented impaired LVDD with preserved LVEF in adult patients with myositis[11,12,13,14,15]. In a controlled, cross-sectional population-based study, Diederichsen, *et al* confirmed that LVDD is a common occurrence in patients with myositis and correlates with disease duration. Moreover, their study documented an association between LVDD and high myocardial 99mTc-PYP uptake, suggesting that inflammation of the myocardium is the underlying pathology[11]. In our case-matched analysis, we did not find any statistically significant difference in LVDD between patients and controls, even if patients with IIM showed an increased prevalence of biventricular (of both RV and LV) diastolic dysfunction.

As for the RV, in our population patients with IIM had a 3.4-fold increased risk to have a subclinical systolic impairment (according to a right GLS < 20%) when compared with controls. To the best of our knowledge, there are few published data related to RV dysfunction in idiopathic PM or DM[11,13,14,15]. In their report, Péter, *et al* documented right systolic and diastolic dysfunction in the acute phase of myocarditis by using TDI and the conventional markers (FAC and tricuspid systolic velocity), with significant improvement in cardiac function after the first 3 months of therapy[15]. In our series, despite longterm treatment, 42% of

patients have RV systolic and diastolic dysfunction that could be linked to repeated myocarditis and/or iatrogenic damage.

Despite the distinctive disease features and pathophysiology, no differences were found in GLS between patients with PM and DM. In PM, a prevalent endomysial infiltrate mainly constituted by CD8+ lymphocyte population affects the MHC Class I–positive muscle fibers, whereas DM is basically a microangiopathy with damage in muscle fibers because of secondary ischemic alterations[1]. Both histopathologic features are encountered in the heart of patients with myositis, involving both the myocardium and the specialized conducting tissue[30,31]. Even though it is presumed that skeletal muscle and heart muscle are affected by the same inflammatory process[30,31], it is possible that other factors such as coronary vasculitis, arterial HTN, and drugs are involved in the development of heart disease in IIM.

In our study, the presence of heart involvement did not correlate with disease duration, active myositis as defined by MITAX, or damage index defined by the MDI. Other studies reported a correlation between LVDD and disease duration[10,11,12,13,14,15]. In particular, Lu, *et al*[13] identified female sex, late onset, and long disease duration as independent risk factors for predicting LVDD in PM/DM. Wang, *et al*[14] further confirmed this link between LVDD and disease duration. In our work, we apparently did not find any correlation between time from diagnosis and any variables used to investigate cardiac involvement. However, ours is a cross-sectional study lacking followup, which cannot allow us to clearly identify the relationship between disease duration and heart dysfunction. Moreover, we focused our attention on the systolic dysfunction that is less described in literature when standard variables for systolic function are used[2,15].

In our population, cardiac disease also seems to be independent of the involvement of other organ systems singly considered. This discrepancy in inflammation of affected organs or in the response to treatment in different organ systems is not surprising, because in DM the cutaneous component of the disease responds poorly to the standard treatment, and often when muscle disease is in remission, the skin manifestation can still be active[28,29].

The effect of the different treatment modalities on heart disease in myositis is a matter of debate. Patients are treated with both standard heart medications (β blockers, calcium antagonists, diuretics, and nitrates) and therapy for the underlying myositis. In the literature, there are few data on a beneficial effect of glucocorticoids and immunosuppressants on the cardiac muscle as on the skeletal[32], while the involvement of human Ig is controversial. On one hand, Ig as an immunomodulatory agent can hinder several mechanisms of inflammation, and its benefit in heart involvement has been documented in systemic lupus erythematosus and in coronaritis in Kawasaki disease[33,34]. On the other hand, the fluid overload linked to IV administration of Ig could be potentially dangerous in patients with heart dysfunction/impairment. It is possible that the use of SC Ig can overcome this problem. Unfortunately, in our experience in 5 patients with myositis and symptomatic heart involvement treated with SC Ig, we found a beneficial effect only in 1 patient having electrocardiographic abnormalities[5]. Thus, the real efficacy of immunomodulating treatment is still to be assessed.

We would like to point out some limitations of our study for which caution is necessary in the interpretation of the results. Weak points are the small sample size, the lack of prospective data, and that the population consisted of patients with different stages of disease activity. However, it is important to consider the rarity of the diseases, the few studies describing the course of cardiac function in myositis, and the recent introduction of strain assessment in clinical practice. Despite the mentioned limits, our data highlight the presence of impaired systolic function in 50% of patients with IIM without cardiac symptoms.

Early detection of systolic dysfunction through longitudinal strain could potentially help to prevent overt, clinically significant heart failure. Through a better and more aggressive management of modifiable risk factors and early treatment (e.g., with inhibitors of the renin-angiotensin-aldosterone system), it is feasible to hypothesize that a significant number of patients showing an impaired GLS would not progress into symptomatic heart failure.

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