SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

Examination of cardiac manifestations of inflammatory muscle diseases

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The PhD Defense takes place at the Lecture Hall of Bldg. A, Department of Internal Medicine, Faculty of Medicine, University of Debrecen
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INTRODUCTION

Idiopathic inflammatory myopathies are rare immune-mediated chronic inflammatory diseases characterized by symmetric and progressive weakness of the proximal muscles. Among them, polymyositis (PM) and dermatomyositis (DM) are characterized by chronic inflammation, fibrosis, damage and destruction of the muscle fibers. The pathomechanism in PM involves perivascular infiltration caused by CD8+ cytotoxic T cells and macrophages, while inflammation and skin rash in DM is mediated predominantly by B cell–dependent humoral mechanisms and T cell–mediated cytokines. Cardiac involvement in DM was first published in 1899 by Oppenheim. Numerous studies have since confirmed that cardiac involvement is common and is one of the main prognostic factors in PM/DM because extramuscular and cardiac manifestations are associated with worse prognosis. Pathologic findings of the myocardium including active myocarditis, mononuclear infiltration, focal fibrosis, vasculitis, intima proliferation, and media sclerosis of the vessels indicate that the heart is a target organ of PM/DM. A metaanalysis (1975–2011; 26 publications, 1530 patients) concluded that the incidence of cardiac involvement in myositis varies between 9% and 72%. The most common clinical syndrome was heart failure in 32%–77% of the patients. Left ventricular (LV) diastolic dysfunction was found in 42% of the patients, while conduction disorders occurred in 25%–38.5% and hyperkinetic LV contraction was seen in 6%–12%. Finally, the cause of death was identified as the direct consequence of heart disease in 46.3% of the patients. Studies suggest that subclinical cardiac manifestations are more common, but details are yet to be clarified. The incidence depends on the applied diagnostic method, patient selection, disease setting, study type, and whether subclinical or clinical manifestations are allowed.

The diagnosis of autoimmune myocardial involvement is difficult; routine electrocardiography (ECG) and laboratory tests complemented with echocardiography, cardiac

magnetic resonance imaging (MRI), and the rarely used endomyocardial biopsy can further improve the diagnostic probability. Few prospective, detailed echocardiographic studies involving large numbers of patients are available in the literature about cardiovascular involvement in this group of patients. These results mainly included early LV diastolic dysfunction, which may serve as a precursor for systolic and diastolic heart failure. Lu and coworkers found in patients with PM/DM that female sex, late onset, and long disease course were 3 independent risk factors in the development of LV diastolic dysfunction. Moreover, Wang, et al demonstrated a significant relationship between the changes in the diastolic variables and the disease duration in patients with DM, similar to what has been shown in rheumatoid arthritis (RA) and systemic sclerosis.

AIMS

In our studies, we aimed to perform a complex cardiac examination of a homogenous, middle-aged, asymptomatic group of IIM patients free of cardiovascular risk factors at diagnosis and prospectively followed.

1. **Aims in our first investigation:**

1.1 To assess structural and functional myocardial abnormalities, systolic and diastolic right and left ventricular functional parameters of newly diagnosed, asymptomatic IIM patients using traditional and new echocardiographic techniques (TDI - tissue Doppler imaging).

1.2Analysis of the non-invasive echocardiographic results found during the 1- and 3-month follow-up depending on the specific therapy.

2. **The aim of our second study** is the 2-year non-invasive echocardiographic follow-up of the IIM homogeneous patient group created in the first study.

2.1. During the 2-year follow-up, we aimed to repeat the echocardiographic examinations, to determine the systolic and diastolic functions of the left and right ventricles and to compare the results to the data obtained in the first examination.

2.2 Analysis and comparison of long-term echocardiographic results in the monophasic and polyphasic groups created on the basis of the clinical course, and the exploration of the possible causes of these results.

PATIENTS AND METHODS

First study

Study population

A total of 30 hospitalized PM/DM patients with recent onset [(23/7), female/male (27/3)] and without clinical cardiac symptoms were enrolled from the Department of Internal Medicine (Debrecen, Hungary) between January 2012 and January 2013, with a mean age of 42.3 ± 1.6 years. All patients fulfilled the criteria of either definitive PM or DM as proposed by Bohan and Peter. Patients were excluded if they presented with malignancy, other systemic autoimmune diseases (RA, systemic lupus erythematosus, mixed connective tissue disease), overlap syndromes, previously diagnosed congenital heart disease, rheumatic fever, hypertension (HTN), coronary artery disease, valvular heart disease, cardiomyopathy, arrhythmias, diabetes mellitus, severe renal disease (serum creatinine level ≥ 130 μmol/l), anemia (hemoglobin ≤ 13.5 g/dl in male, ≤ 12.0 g/dl in female), atrial fibrillation, or mitral regurgitation exceeding moderate severity. The patients were thoroughly examined at the time of diagnosis (0 month), when anamnestic data were collected, physical examination involving blood pressure measurement and ECG was performed, and blood samples were collected for

routine and special autoimmune laboratory tests. Finally, echocardiographic examination was performed, obtaining a dataset with conventional and TDI measurements. Thereafter, specific therapy began and the same echocardiographic examinations were repeated 1 month and 3 months after the diagnosis. An age-matched healthy population served as control (mean age 44.4 ± 0.9 yrs).

Clinical characteristics

Detailed records of clinical information were made at onset, including age, blood pressure, heart rate, muscle disease activity, presence of lung involvement, and Raynaud sign. Muscle disease activity was evaluated according to the Myositis Disease Activity Assessment Tool (MDAAT, version 2, 2005) by physician assessment using a visual analog score (VAS). High-resolution computed tomography of the lungs was performed to investigate radiographic abnormalities [pulmonary infections, fibrosis, tuberculosis, and interstitial lung disease (ILD)]. Laboratory assessment performed on the first day of hospitalization included, among other items, total cholesterol, triglyceride, blood glucose, uric acid, total creatine kinase (CK), and an autoimmune panel (anti-dsDNA, anti-SRP, anti-Scl-70, and myositis profile 3 Blot Strip: Ro52, OJ, EJ, Pl-12, Pl-7, SRP, anti-Jo1, PM-Scl75, PM-Scl100, Ku, and Mi-2B). After the diagnosis was established, specific therapy involved high-dose (0.5-1-2-3 mg/kg/day) corticosteroid (prednisolone or methylprednisolone) for 4 weeks, which was tapered gradually (in 10 weeks, decreased by 4 mg/week). We used proton pump inhibitors, potassium, and diuretic (furosemide) to prevent the side effects of corticosteroids (gastrointestinal ulcers, bleeding, hypokalemia, and fluid retention) as supplementary therapy. Beta blockers were also needed in 30% of the cases. Second-line treatment was introduced when a patient's general condition deteriorated despite having taken corticosteroids or when severe dysphagia or lung fibrosis occurred. Cyclosporine (5 mg/kg/day, reduced for 2.5 –3.5 mg/kg/day after 1–2 mos) was added to the corticosteroid therapy in patients with ILD and no improvement while taking steroids.

Second study

Study population

During the second study, we followed the same patient group for 2 years as in the first study. Among the 30 IIM patients (female/male: 27/3), 2 patients dropped out during the follow-up. One of them developed new ECG abnormalities (RV strain signs and PM/SSc syndrome with confirmed pulmonary hypertension, while the other patient developed breast cancer.) During the follow-up, the patients were divided into two groups: monophasic (n = 16) and polyphasic (n = 12) groups. Patients in the monophasic group did not experience deterioration and received steroid therapy, while relapses occurred during the follow-up period in the polyphasic group. The echocardiographic results in the different groups were compared to the age- and gender-matched healthy control group (n = 26). During the 2-year follow-up, another physical examination, blood pressure measurement, ECG and echocardiography were performed. In addition to routine laboratory tests, the autoimmune panel (anti-dsDNA, anti-SRP Strip: Ro52, OJ, EJ, Pl-12, Pl-7, SRP, anti-Jo1, PM-Scl75, PM-Scl100, Ku, and Mi-2B) was re-evaluated using the membrane fixed blot technique (Euroline Myositis Antigen Profle4, EuroImmun, Lübeck, Germany) based on laboratory instructions.

Clinical characteristics

Autoimmune profile confirmed at the time of the diagnosis did not change (anti-Jo 1: 20 %, anti-PM/Scl-100: 3.3 %). New therapy released during the 24 months as follows: methotrexate: 16.6 %, cyclophosphamid: 6.6 %, rituximab: 6.6 %), however steroid was administered in 100 % of the cases. 7/30 patients had mild hypertension (mean systolic RR: 140±5 Hgmm, mean diastolic RR: 90±3 Hgmm). New-onset diabetes could not be detected during the follow-up period.

Methods

Conventional echocardiography

Transthoracic echocardiography was performed using ultrasound equipment (Acuson Sequoia, Siemens AG) with a 1–5 MHz transducer. All measurements were carried out by a single observer blinded to patient/control status. All patients were examined in the standard left parasternal and apical windows with normal breathing. Left atrial (LA) diameter, LV end-diastolic and end-systolic diameters were determined with 2D and M mode echocardiography based on the criteria of the European Association of Echocardiography. LV ejection fraction (EF) was calculated according to the Simpson method. Mitral inflow velocities were evaluated by pulsed-wave Doppler imaging on the apical 4-chamber view with the sample volume placed at the tip of the mitral leaflets. Peak early (E) and peak late diastolic transmitral flow velocities (A) were measured and E/A ratio was calculated to characterize LV diastolic function. Moreover, the early transmitral flow deceleration time (DT), a further marker of LV diastolic function, was also measured. RV function was described by the fractional area change [RV FAC: (end-diastolic RV area — end-systolic RV area)/end-diastolic RV area].

Mitral annulus plane systolic excursion (MAPSE) and tricuspid annulus plane systolic excursion (TAPSE) were measured by M mode to determine the longitudinal function of the left and right ventricle, respectively. TAPSE was calculated by placing the M mode cursor through the tricuspid annulus in a standard apical 4-chamber window and the longitudinal excursion of the endocardial surface between end-diastole and end-systole was measured. MAPSE was obtained by similar method in the mitral annulus.

Pulmonary artery systolic pressure (PASP) was calculated with the measurement of the tricuspid regurgitation peak velocity in those patients who had some degree of tricuspid regurgitation. In the absence of obstruction to RV outflow tract, RV systolic pressure equals

PASP. Mean values of measurements from 3 consecutive beats were calculated for further analysis.

TDI measurements:

All TDI measurements were performed in adherence to the guidelines and standards of the European Society of Echocardiography. TDI uses Doppler principles to measure the velocity of myocardial motions: peak myocardial systolic velocity (s), early myocardial diastolic velocity (e′) and late myocardial diastolic velocity (a′). Pulsed wave tissue Doppler was performed in both groups with a frame rate of about 60/s. TDI data were obtained from the lateral site of the mitral and tricuspid annulus. The s velocity at the lateral annulus is a good measure of the longitudinal systolic function. In the absence of regional wall-motion abnormalities, TDI velocities obtained from the posterior and septal mitral annuli do not provide further information about the ventricular function, therefore only the velocities of the lateral sites were recorded. The e′ velocity of the mitral and tricuspid annulus is an established indicator of LV and RV myocardial relaxation, respectively. When myocardial relaxation is impaired because of aging or a disease process, e′ is less or not at all affected by the preload. The a′ velocity of the mitral annulus has been correlated with LA function, which is increased in early diastolic dysfunction, and decreases when atrial function deteriorates. Moreover, E/e′ ratio, a preload-independent factor, can be applied for the estimation of the LV filling pressure. $E/e' \leq 8$ indicates normal LV end-diastolic pressure.

Statistical analysis: Numerical data in this report are given as mean values ± SEM. D'Agostino-Pearson normality test was used to test whether the data showed a Gaussian distribution. The Kruskal-Wallis test or ANOVA followed by the Bonferroni posthoc test were used to compare the different groups, with p values <0.05 considered statistically significant. Statistical analyses were performed with GraphPad Prism 5.02 software (GraphPad Software Inc.)

RESULTS

First study.

Baseline characteristics.

Of the 30 patients, 23 had PM and 7 had DM. The study population was chosen randomly and matched the general prevalence findings in our country. The patients did not have HTN. Physiologic mean blood pressure was recorded (systolic RR: 120 ± 2 mmHg, diastolic RR: 76 ± 1 mmHg), and the mean heart rate was 85 ± 1 beats/min. Neither specific findings during physical examination nor ECG abnormalities were found.

Echocardiographic findings.

At the time of diagnosis, chamber diameters — similarly to those in the control group — were in the normal range and remained unchanged during the follow up period. Echocardiographic measurements were done to evaluate the systolic and diastolic function of the LV and RV.

LV systolic function.

Global systolic function of the LV was characterized by the traditionally used variable, the EF measured by the Simpson method, which was in the normal range, suggesting normokinetic LV throughout the 3 months. The longitudinal LV systolic function (MAPSE) assessed by M mode increased significantly for the third month compared to the baseline value. Additionally, LV systolic function measured by the more sensitive and detailed TDI method showed major changes: the mean mitral lateral systolic velocity (lateral s) was significantly lower than that of the controls; it increased to the control level in the following 3 months. These traditionally measured data suggest a physiological global systolic LV function; nevertheless, an initial deteriorated LV systolic function was observed by the TDI method. The function improved parallel with the administration of the immunosuppressive therapy.

LV diastolic function.

LV diastolic function was evaluated by the characterization of the transmitral inflow Doppler pattern (E/A ratio, DT) and the TDI measurement of the lateral segment of the LV myocardium (lateral e′ and a′ velocities). E/A ratio calculated from the Doppler trace of the transmitral inflow fit the normal range at the time of the diagnosis with significant decrease thereafter. In line with this variable, DT increased significantly during the follow-up period. In parallel, the early diastolic lateral myocardial relaxation velocity (lateral e′) decreased significantly for the first month of the follow-up period, and showed a decreasing tendency compared to the control in the third month. The late diastolic lateral myocardial relaxation velocity (lateral a′) was significantly higher in the third month compared both to the healthy controls and to the baseline value of the patients with PM/DM. E/e′ ratio — calculated from the mitral inflow E velocity and the TDI lateral e′ velocity — is commonly used to estimate the LV filling pressure. At the time of the diagnosis the finding in the patients with PM/DM was similar to that in the controls. This value increased significantly during the follow-up period; however, it did not reach the cutoff value of 8, which would suggest an elevated LV filling pressure.

These data show that diastolic dysfunction occurred during the follow-up period; however, no significant correlation could be established between the diastolic variables and disease activity assessed by MDAAT VAS score (E/A: r2 = 0.7181, p = 0.3563; E/e′: r2 = 0.6961, p = 0.3717).

Pulmonary artery systolic pressure and RV function

Pulmonary HTN could not be found in our study population: the average PASP was 34.17 ± 1.91 mmHg and it did not change significantly during the 3 months (34.71 ± 1.61; 34.12 ± 1.81, 1 and 3 mos, respectively), indicating normal PASP, thereby pulmonary HTN is unlikely during the 3-month follow-up period in our study population. RV systolic function characterized by the FAC significantly improved during the 3 months compared to the baseline value below the physiological range. In line, the longitudinal RV systolic function (TAPSE)

increased significantly for the third month compared to the initial value. Moreover, the tricuspid annular systolic velocity (tricuspid s) was significantly reduced in the patients with PM/DM compared to the control group at any time, but it increased significantly during the follow-up period, approaching the control normokinetic RV systolic function. The tricuspid early diastolic velocity (tricuspid e′) — characterizing RV diastolic function — showed opposite changes compared to the lateral e′ in the left heart, from a subnormal level in patients with PM/DM at the time of the diagnosis, it increased significantly for the first month of follow-up. Also, tricuspid a′ velocity showed a tendency to increase in the patient group, but the differences did not reach the level of significance. Besides the LV, both the systolic and diastolic function of the RV seem to be affected in patients with PM/DM.

Second study

Clinical characteristics

Data of 28 IIM patients were evaluated, who completed the study. The mean age at diagnosis was 41.9 ± 1.6 years, the female/male ratio was 25/3. Autoimmune profile confirmed at the time of the diagnosis with myositis profile 3 Blot Strip (anti-Jo 1: 6/28, anti-PM/Scl-100: 1/28, anti-PM-scl-75: 3/28) was re-evaluated with line blot assay (Euroline Myositis Antigen Profle4) and we could detect 4 new autoantibody positivity (1 anti-Mi2, 1 anti-TIF1γ, 2 anti-NXP2). New therapy was released during the 24 months as follows: methotrexate in 5 cases, cyclophosphamide in 2 cases and rituximab in 2 cases; however, steroid was administered in 100% of the cases. The mean blood pressure (130/78±1 mmHg) was slightly higher at the end of the follow-up period, compared to baseline and control; hence, 7/28 patients had mild hypertension at the end of the study. New-onset diabetes could not be detected during the follow-up period.

Echocardiographic findings.

The right atrial (RA: 29.9±0.5 mm, 30.5±0.7 mm, 31.9±1.1 mm, 29.9±0.8 mm) and right ventricular dimensions (RV1: 25.6±0.3 mm, 26.7±0.8 mm, 26.8±1.3 mm, 27.8±1.4 mm; RV2: 26.0±0.7 mm, 25.2±0.7 mm, 28.1±2.4 mm, 27.2±1.1 mm; RV3: 55.6±1.1 mm, 57.3±1.8 mm, 56.5±2.4 mm, 50.3±2.8 mm; RVSA: 9.4±0.3 cm^2 , 11.0±0.8 cm2 , 9.3±0.4 cm^2 , 9.3±0.5 cm^2 ; RVDA: 17.1±1.1 cm^2 , 16.5±0.6 cm^2 , 16.6±0.7 cm^2 , 17.3±0.9 cm^2 ; control, baseline, monophasic, polyphasic, respectively) were in the normal range and did not change compared either to the controls or to the baseline during the follow-up. LV diameters were also in the normal range. We could not detect any significant changes in LVESD (30.0±0.9 mm, 28.2±0.8 mm, 34.6±2.4 mm, 30.3±1.4 mm; control, baseline, monophasic, polyphasic, respectively), or in the LVEDD (49.3±1.0 mm, 47.1±1.1 mm 44.0±1.8 mm, 50.3±1.4 mm; control, baseline, monophasic, polyphasic, respectively).

LV systolic function

Global systolic function of the LV was characterized by the traditionally used parameter, the EF measured by the Simpson's method. We detected a significantly impaired LVEF in both subgroups at the end of the follow-up compared to the controls; however, it was more pronounced in the polyphasic group where it was significantly lower than the baseline or the monophasic group (62.6±0.6%, 60.9±0.9%, 58.1±0.6%, 51.7±0.7%; control, baseline, monophasic, polyphasic, respectively). The longitudinal left ventricular systolic motion (MAPSE) assessed by M-mode decreased significantly during the 2 years in patients with polyphasic disease patterns compared to the baseline and the control group (18.5±0.6 mm, 18.0±0.7 mm, 17.7±1.0 mm, 14.5±0.6 mm; control, baseline, monophasic, polyphasic, respectively). LV systolic function measured by the TDI method showed major changes: the mitral lateral systolic velocity (lateral s′) was significantly lower in both subgroups at 2 years than at the time of the diagnosis; moreover, the polyphasic group was found to have a

remarkable decreased s′ velocity (10.4±0.3 cm/s, 8.6±0.4 cm/s, 8.6±0.4 cm/s, 6.4±0.4 cm/s; control, baseline, monophasic, polyphasic, respectively).

The above findings confirm a subclinical left ventricular dysfunction in both subgroups at the end of our study, which could also be detected by the TDI method at the beginning of the disease progress.

LV diastolic function

LV diastolic function was evaluated by the characterization of the transmitral inflow Doppler pattern (E/A, DT) and the TDI measurement of the lateral segment of the LV myocardium (lateral e′ and lateral a′ velocities). Any diastolic abnormalities could not be detected at baseline; however, a grade I diastolic dysfunction appeared both in the monophasic and polyphasic group: significantly lower E/A ratio, a longer DT were measured in the polyphasic and the monophasic group compared to the controls and the baseline timepoint (E/A ratio: 1.33±0.02, 1.32±0.1, 0.84±0.06, 0.68±0.04; DT: 144.7±3.2 msec, 158.3±5.7 msec, 182.8±15.4 msec, 190.8±7.6 msec; control, baseline, monophasic, polyphasic, respectively). Accordingly, the early diastolic lateral myocardial velocity (lateral e′) decreased (12.9±0.2 cm/s, 12.3±0.6 cm/s, 8.7±0.9 cm/s, 7.4±0.3 cm/s; control, baseline, monophasic, polyphasic, respectively) and the late diastolic myocardial velocity (lateral a′) increased significantly in the two disease groups at the end of the follow-up period (10.7±0.3 cm/sec, 11.1±0.8 cm/s, 15.4±1.2 cm/s, 17.3±0.8 cm/s; control, baseline, monophasic, polyphasic, respectively). E/e′ ratio - calculated from the mitral infow E velocity and the TDI lateral e′ velocity is commonly used to estimate the LV filling pressure. The E/e′ ratio was significantly higher in both groups compared to the controls and the baseline (5.8±0.2, 5.0±0.2, 8.7±0.6, 9.0±0.4; control, baseline, monophasic, polyphasic, respectively).

These results show that diastolic dysfunction (grade I – impaired relaxion) appears both in the monophasic and polyphasic groups. Larger LA diameter supports a further impairment

of the diastolic function in the polyphasic group (32.1±0.6 mm, 32.2±0.7 mm, 33.3±0.8 mm, 37.8±0.6 mm; control, baseline, monophasic, polyphasic, respectively).

RV function and pulmonary artery systolic pressure

FAC, TAPSE and the tricuspid systolic velocity (tricuspid s′) were used to characterize RV function. At baseline attenuated FAC and tricuspid s′ velocities could be measured showing a depressed global RV systolic function (FAC: 45.6±1.8%, 37.0±1.5%, 41.0±1.6%, 32.7±1.4%; tricuspid s′: 13.1±0.3 cm/s, 9.6±0.4 cm/s, 9.3±0.5 cm/s, 7.8±0.2 cm/s; control, baseline, monophasic, polyphasic, respectively); however, the longitudinal RV systolic function was similar to the control group (TAPSE: 22.7±0.5 mm, 22.3±0.7 mm, 21.3±0.7 mm, 18.1±0.3 mm; control, baseline, monophasic, polyphasic, respectively). RV systolic function did not decline further in the monophasic group at the end of the follow-up period; however, an additional deterioration was detected in the polyphasic group as demonstrated by the further decline in each systolic RV parameters. Additionally, an RV diastolic dysfunction was also found in the three disease groups which was the most pronounced in the polyphasic subgroup, characterized by the decrease in the tricuspid early diastolic velocity (tricuspid e′: 13.3±0.5 cm/s, 10.7±0.6 cm/s, 9.4±0.7 cm/s, 7.2±0.3 cm/s; control, baseline, monophasic, polyphasic, respectively) and the increase in the tricuspid late diastolic velocity (tricuspid a’: 11.5±0.4 cm/s, 14.6±0.9 cm/s, 14.3±0.9 cm/s, 15.1±0.7 cm/s; control, baseline, monophasic, polyphasic, respectively), similarly as observed in the left heart. These findings present a subclinical RV systolic dysfunction (FAC, TAPSE, tricuspid s′) and a RV diastolic dysfunction (tricuspid e′, a′) which was the most severe in the polyphasic group at the end of the study. We could not detect any direct, or indirect echocardiographic signs of pulmonary hypertension, in either group.

DISCUSSION

(Based on the results of both studies)

Our first study, to our knowledge, is the first longitudinal study to detect systolic dysfunction LV and RV using the TDI method at the time of diagnosis in middle-aged IIM patients who are asymptomatic and do not have cardiovascular disease. Systolic dysfunction detected in the initial phase improved significantly during the follow-up period while patients were treated with immunosuppressive therapy. At the same time, our echocardiography results confirmed diastolic dysfunction, which is consistent with the results of other investigators.

Conventional echocardiography measurements initially showed physiological right ventricular, left ventricular and atrial diameters, as well as normokinetic left ventricular systolic function. However, the lateral annulus systolic rate (s') measured by the more sensitive TDI method indicated subclinical left ventricular systolic dysfunction. This variable returned to normal after 3 months of specific therapy. As with left ventricular variables, right ventricular systolic dysfunction was reflected in a decrease in systolic rate in the tricuspidal annulus and FAC (Fractional area change) observed at baseline. The tricuspidal annulus systolic rate (S') and FAC returned to normal by the end of the follow-up period, similar to changes in left ventricle. Interestingly, although physiological left ventricular diastolic function was found at the time of the diagnosis, diastolic dysfunction developed during the follow-up period, which was reflected in decreased e′ velocity, decreased E/A ratio, and significant increases in DT to E/e′ ratio. The increasing E/e′ ratio did not exceed the upper end of the physiological range, indicating normal left ventricular filling pressure at this point in time.

The above changes in echocardiographic diastolic variables at the end of the 3-month follow-up period corresponded to grade 1 diastolic dysfunction with normal filling pressure (A $\geq$ E, E/e′ $\leq$ 8, normal LA diameters). The increase in tricuspid e′ and the decreasing trend in

tricuspid annulus velocity indicated markedly different changes in the right ventricle. This refers to the different behavior of the right ventricle; however, no other right ventricular diastolic variables were investigated (e.g. tricuspid E/A, DT). More detailed studies involving a large number of patients are needed to more accurately assess right ventricular diastolic function. Our results can be considered as important initial steps in demonstrating myocardial involvement in IIM.

Our second study was planned longitudinally, the patients of the first study were followed for 2 years. During the follow-up, patients were divided into monophasic and polyphasic groups according to the course of the disease, according to whether they responded well to the applied therapy after a relapse or whether recurrent relapses dominated the picture during the clinical course and another therapeutic supplement became necessary.

Different echocardiography results were found according to the course of the disease in the two groups (monophasic vs. polyphasic).

In line with other studies, time-related left ventricular diastolic dysfunction (grade I) appeared in both monophasic and polyphasic groups during follow-up. However, there is no significant difference in dystolic dysfunction between the subgroups of the disease, although a higher LA and LVEDD value in the polyphasic group may indicate a predisposition to more severe diastolic function. In parallel with left ventricular changes, right ventricular diastolic dysfunction appeared in both mono- and polyphasic groups, more severe in the polyphasic group, as shown by significantly lower tricuspid e′ velocity compared to controls. As a key result, at the end of the study, subclinical left (EF, MAPSE, lateral s) and right ventricular (FAC, TASE, tricuspid s') systolic dysfunction was observed in both subgroups of IIM patients. Our results suggest significantly more severe left and right ventricular systolic dysfunction in the polyphasic group 2 years after diagnosis. In the early stages of the disease, echocardiographic tissue Doppler (TDI) results revealing systolic dysfunction in LV and RV may be early signs

of heart involvement, indicating acute myocarditis or myocardial oedema. After 3 months of follow-up where patients received high doses of steroid therapy, normalization of lateral and tricuspidal annulus systolic rates as measured by TDI may indicate a decrease in cardiac edema, primarily in response to steroid therapy. In 25–30% of patients with autoimmune myositis, previous autopsy data on myocarditis support this view. Diastolic dysfunction during steroid therapy may be the first sign of myocardial fibrotic transformation. Early echocardiographic diastolic abnormalities (changes in E/A, E/e′) were not correlated with muscle strength score, similar to results from previous investigators who found no association between echocardiographic variables and clinical features, laboratory results, or ILD .Sharratt and colleagues demonstrated a linear relationship between muscle weakness and cardiac symptoms, disease activity, and systolic time intervals on ECG in 5 patients.

One possible explanation for conflicting data may be differences between patient populations and/or study methods. Further prospective studies would be needed to explore possible links between disorders of skeletal muscles and the heart. The exact molecular and cellular mechanisms of left ventricular diastolic dysfunction have not yet been elucidated, but these diastolic abnormalities indicate intrinsic myocardial manifestation during the follow-up period. Gupta and colleagues commented on the role of myocardal fibrosis and recurrent myocarditis. In addition, vascular factors such as vasculitis, intimal hyperplasia or coronary tunica media sclerosis may also play a role in IIM. In addition, specific autoantibodies (anti-Jo, anti-Ro-52 and anti-Ro-60) promote the production of interferon α, causing direct myofiber destruction. Other inflammatory factors can also contribute to the development of diastolic dysfunction. For example, interleukin 6 (IL-6), IL-1β, and tumor necrosis factor (TNF)-α may cause myocyte damage via MHC-1 with local nitric oxide release and myocardial fibrosis .LV diastolic dysfunction observed in the third month after diagnosis is consistent with previous results from other investigators. Lu et al. and Wang, et al reported more severe diastolic

dysfunction after mean disease durations of 4.78 and 11.12 months in similar age groups. In a later study, Wang and colleagues often found left ventricular diastolic dysfunction in DM patients with no apparent cardiovascular disease and reported an association between changes in transtmitral flow and disease duration. A longer duration of the disease appears to correlate with persistent cardiomyocyte damage, pathological calcification, and high concentrations of cytokines (e.g., vascular cell adhesion molecule, TNF-α). If the changes found with early echocardiographs show progression, then recurrent inflammation, myocardial fibrosis .and consequent diastolic dysfunction appear.

The basic disorder of the heart muscle is inflammation with necrosis and fibrosis, regardless of the course of the disease, similar to pathological changes in skeletal muscles. In addition, over the past few years, there has been increasing evidence that accelerated atherosclerosis can be confirmed in patients with IIM, which has been confirmed by a variety of non-invasive methods and biomarkers. Systemic and local inflammation can either produce direct effects in the heart muscle or make the heart more sensitive to conventional risk factors. Vascular changes affecting coronary arteries have also been reported, such as vasculitis, intima proliferation, media sclerosis, and microvascular disease associated with vasospastic angina.

Other pathophysiological mechanisms, e.g. increased ventricular stiffness caused by fibrosis or disturbances in calcium regulation, can also cause LV diastolic and systolic insufficiency. The exact molecular and cellular mechanisms of myocardial dysfunction in IIM have not yet been elucidated. More rarely, the development of severe systolic dysfunction of the left or right side of the heart indicates irreversible changes, with the occurrence of severe cardiovascular pathologies (acute fulminant myocarditis, mitral chordae tendineae rupture, or acute right heart failure) affect cardiac morbidity and mortality in patients with IIM. In this group of patients, cardiac outcome depends on many determinants, such as age at the onset of the disease, gender, activity of the disease, time of diagnosis and time of initiation of specific

therapy, subtype of disease, autoimmune antibody profile, from associated cardiovascular and lung diseases, as well as toxic side effects of therapy. These factors may all contribute to the progression of diastolic dysfunction. The characterization of the inflammatory process in the heart muscle associated with systemic autoimmune diseases, in our case IIM, has indisputable clinical significance. Only a small percentage of patients with IIM suffer from clinical heart disease, but heart involvement is one of the leading causes of death, and early detection in subclinical situations remains a challenge. These results highlight the importance of newer, more sensitive echocardiography techniques, such as TDI and strain rate imaging, 3DE, in identifying early signs of cardiac involvement in IIM, which is a determining prognostic factor in these diseases.

IIM patients are usually divided into four subgroups based on the course of the disease: acute fulminant, monophasic, polyphasic and chronic progressive forms. We included monophasic and polyphasic groups in our study, as it was almost impossible to collect data from patients with acute fulminant disease, and there was not enough time to include patients from the chronic progressive group. According to the definition, no new deterioration (relapse) appears in the monophasic group after the first therapy, while polyphasic patients are characterized by multiple relapses. More than half of relapses typically occur within the first 2 years of maintenance therapy. Its severity ranges from subclinical CK elevation to severe clinical relapse. Although the relapse rate does not change in DM and PM, multiple relapses are more common in DM. The incidence of relapses is not related to the initial severity of the disease or to the time between diagnosis and the start of treatment. Based on the results of our studies, subclinical left and right ventricular dysfunction was found after 2 years of IIM disease persistence. More severe subclinical left and right ventricular systolic dysfunction can be demonstrated in the polyphasic group. Therefore, with emphasis on mandatory cardiac screening proposed by guidelines, this group should receive increased attention.

MR and modern echo diagnostics

There is growing evidence that non-invasive imaging and newer echo techniques, including TDI, strain rate imaging and 3DE, and cardiac MRI, contribute to the diagnosis of myocarditis at the subclinical stage and help initiate specific treatment. Myocardial inflammation in the early stages is not detected by conventional echocardiography or nuclear techniques, since they are unable to detect small changes in tissue structure associated with cardiac edema, including myocardial edema, cell infiltration and fibrosis, which usually take place without concomitant changes in left ventricular function. MRI of the heart can detect tissue changes in the early stages of myocarditis. The best imaging method for LGE is "late gadolinium enhancement." This gold standard method is suitable for in vivo evaluation of myocardial scar. It was in excellent agreement with histology and ideal for detecting areas of necrosis that cannot be detected by single photon emission CT or positron emission tomography (PET). This technique is used to detect myocardial damage sensitively, indicating the degree and location of myocardial inflammation and fibrosis better than myocardial scintigraphy or echocardiography. Cardiac MRI can predict or rule out myocarditis (edema, increased membrane permeability or capillary membrane permeability and fibrosis) with 78% diagnostic accuracy, and fibrosis can be distinguished from ischemic necrosis with 78% diagnostic accuracy. In addition to echocardiography, CMR is the best choice for diagnosing myocarditis and fibrosis.

The diagnosis of inflammatory myocarditis diagnosed with CMR shows 3 tissue characteristics: myocardal edema, capillary leakage and fibrosis. CMR is able to distinguish between myocardial infarction and inflammation, since the subendocardial layer is not affected in the inflammatory tissue. Several smaller studies (14–26 patients) have confirmed the role of CMR in detecting myocardial involvement in IIM in asymptomatic patients.

Mavrogeni et al. reported epicardial and intramyocardial late gadolinium accumulation (LGE) in 56.3% (mean age: 44 years, CV without clinical signs, 24 months follow-up) of the 16 IIM patients studied, characteristic of previous inflammation with normal LV volume and normal LVEF. Khoo et al. reported LGE in 9/19 asymptomatic IIM patients with CMR, myocardial inflammation, fibrosis or infiltration can be patchy, sub-epicardial, and mid-myocardial. The emergence of new echocardiographic methods such as TDI, strain rate imaging, and 3D echocardiography has dramatically expanded the scope of echocardiography, providing accurate assessments of regional contractility, myocardial blood flow, microvascular integrity, and longitudinal myocardial function. The disadvantages of echocardiography include operator dependence, poor acoustic window, reduced appreciability in case of obesity or lung disease, and lower reproducibility. However, compared to cardiac MRI, echocardiography is a simple, inexpensive, non-invasive, bedside technique for evaluating ventricular function.

Recurrent acute myocarditis and acute myocardial edema during the disease process may cause clinical or subclinical left and right ventricular systolic dysfunction, resulting in subepicardial late contrast stacking on cardiac MRI and TDI and strain rate imaging can be detected by new imaging echocardiography methods. The traditional echocardiographic systolic parameter LVEF is a commonly used parameter to measure changes in systolic function; however, more sensitive echocardiography techniques, such as TDI and strain rate imaging, are more suitable and sensitive methods for detecting subclinical systolic dysfunction. Guerra et al. used the two-dimensional strain rate imaging method for the first time in 28 asymptomatic patients with myositis (mean age: 61.3±13.1 years) and showed significantly lower RV global systolic strain values (RVGLS) and LV global systolic strain (LVGLS) compared to controls. Zhong et al. published a three-dimensional strain rate echo study in 60 IIM patients (excluding clinical manifestations of coronary artery disease, mean age: 51.1±12.6

years) with significantly lower rates of LVGLS and RVGLS. In addition, myositis damage index has been associated with LVGLS and RVGLS.

These results correlate with our TDI results showing subclinical left and right ventricular dysfunction after 2 years of IIM disease. Based on our initial studies, observed subclinical dysfunction may be reversible in IIM patients treated with specific drugs (high-dose steroids and immunosuppression). This was confirmed by Allanore et al. in a small number of cases, CMR, based on a decrease in late contrast enhancement.

No studies have compared echocardiography with CMR abnormalities in IIM. Definitive conclusions would require further prospective follow-up studies involving a larger number of patients and multimodal imaging.

However, our TDI echocardiography results have limitations. Our study population is quite small, and a larger number of patients would be needed to refine our results. Autoimmune myocardial involvement is difficult to identify due to nonspecific ECG signals, subclinical echocardiography disorders and nonspecific lab results (elevated cTnT, CK).

As mentioned above, cardiac MRI can help detect acute myocarditis. Endomyocardial biopsy is the gold standard for diagnosis, but is not routinely used as an invasive procedure. A minor limitation of TDI measurement in our study is that tissue Doppler test results are angle-dependent. To avoid errors, all variables were measured in 3 independent heart cycles and an average was calculated.

The TDI method appears to be appropriate for detecting early functional myocardial changes indicating cardiac involvement in systemic autoimmune disease. A rheumatologist, immunologist and cardiologist should take this into account, since echocardiography is a non-invasive, safe, generally available and relatively cheap technique.

SUMMARY

In our recent work we intended to prospectively study a homogenous, middle aged patient group diagnosed with idiopathic inflammatory myopathies (IIM) without cardiovascular risk factors and symptomes. Long term cardiac parameters were assessed using traditional echocardiography and tissue doppler imaging techniqe.

In our first study we included 30 IIM patients and 28 age and sex matched healthy controls. We detected left and right ventricular systolic dysfunction at the time of the IIM diagnosis, which improved at the end of the 3 months follow-up period in parallel with the steroid treatment of the myositis. Furtheremore, measurements indicated the development of diastolic dysfunction in the patients at 3 months.

In our second study the same patient cohort was followed for two years. Patients with monophasic/polyphasic disease patterns were studied separately and compared to age-matched healthy individuals. We could detect subclinical left and right ventricular dysfunction in patients with polyphasic disease course 2 years after diagnosis, which resulted a grade I. left ventricular dyastolic dysfunction. Similar, but not signifcant tendencies could be detected in patients with monophasic disease patterns.

Our results argue for that there are subclinical left and right ventricular dysfunctions at the beginning of the myositis, which are the consequences of myocardial edema and acut myocarditis and improve after specific treatment. In patients with polyphasic disease course, relapsing subclinical myocarditis result left and right ventricular systolic dysfunctions 2 years after diagnosis, which identifes them as a high-risk population, requiering close cardiologic follow-ups and individual treatment.

It seems that tissue doppler imaging is a useful method to detect cardiac abnormalities in IIM complementing conventional echocardiography and can recognize the high cardiac risk, which can result the decrease of myositis related cardiovascular mortality in the patients.

NEW SCIENTIFIC ACHIEVEMENTS

1. When IIM disease is diagnosed, mild subclinical left and right ventricular systolic dysfunction can be confirmed on the basis of echocardiographic examinations performed on a middle-aged patient group free of cardiovascular risk factors.

2**.** During 3 months of follow-up, with specific immunosuppressive therapy, systolic functional parameters of the left and right ventricles returned to normal.

3. During 3 months of follow-up, mild diastolic dysfunction appeared in both the left and right ventricles.

4. After 2 years of IIM patient follow-up, subclinical left and right ventricular systolic dysfunction with grade I diastolic dysfunction can be demonstrated in the polyphasic group.

5. Based on differences found during 2 years of follow-up, the polyphasic group is considered to be a higher risk population within the IIM group and requires closer cardiological control

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Candidate: Andrea Péter
Doctoral School: Gyula Petrányi Doctoral School of Allergy and Clinical Immunology

List of publications related to the dissertation

1. **Péter, A.**, Balogh, Á., Csanádi, Z., Dankó, K., Griger, Z.: Subclinical systolic and diastolic myocardial dysfunction in polyphasic polymyositis/dermatomyositis: a 2-year longitudinal study.
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