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Myocardial fibrosis detected by magnetic resonance in systemic sclerosis patients – Relationship with biochemical and echocardiography parameters

Milan Hromádka [a,1], Jitka Seidlerová [b,c,*,1], David Suchý [d], Daniel Rajdl [e], Jan Lhotský [a], Jaroslav Ludvík [f], Richard Rokyta [a], Jan Baxa [f]

[a] Cardiology Department, University Hospital and Faculty of Medicine in Pilsen and Faculty Hospital, Charles University, Czech Republic
[b] Internal Department II, University Hospital and Faculty of Medicine in Pilsen, Charles University, Czech Republic
[c] Biomedical Centre, Faculty of Medicine in Pilsen, Charles University, Czech Republic
[d] Department of Clinical Pharmacology, Rheumatology, University Hospital and Faculty of Medicine in Pilsen, Charles University, Czech Republic
[e] Department of Clinical Biochemistry and Hematology, University Hospital and Faculty of Medicine in Pilsen, Czech Republic
[f] Department of Imaging Methods, University Hospital and Faculty of Medicine in Pilsen, Charles University, Czech Republic

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ABSTRACT

Objectives: Systemic scleroderma (SSc) is a rare connective tissue disease presenting with fibrosis affecting skin and internal organs. Cardiovascular magnetic resonance (CMR) with quantification of extracellular volume (ECV) and T1 mapping might help to detect heart involvement. We aimed to evaluate whether myocardial involvement correlates with functional and laboratory parameters.

Methods: Thirty-three asymptomatic SSc patients (29 women, aged 56.6 ± 12.2 years) and 20 controls (10 women, 53.7 ± 13.1 years) were examined using CMR, echocardiography, functional pulmonary test and laboratory assessment.

Results: SSc patients had higher ECV (27.5 ± 2.8 vs. 22.8 ± 1.9%, $P < 0.0001$) and native T1 values (1258.9 ± 51.2 vs. 1192.2 ± 32.6, $P < 0.0001$) compared to controls. Plasma level of growth differentiation factor 15 (GDF-15) and galectin-3 correlated with ECV ($r = 0.35$; $P = 0.0076$ and $r = 0.38$; $P = 0.0081$) and native T1 ($r = 0.31$; $P = 0.023$ and $r = 0.35$; $P = 0.012$). GDF-15 was also negatively correlated with diffusing capacity of the lung for carbon monoxide ($r = -0.58$; $P = 0.0004$) and positively correlated with modified Rodnan skin score ($r = 0.59$; $P = 0.0003$). Conventional echocardiography parameters were similar in SSc patients and controls. However, the global longitudinal peak systolic strain (GLPS) was lower in SSc patients compared to controls (18.6 ± 1.6 vs. 21.1 ± 1.2%; $P < 0.0001$). GLPS also negatively correlated with native T1 ($r = -0.35$; $P = 0.0097$), ECV ($r = -0.33$; $P = 0.014$), GDF 15 ($r = -0.31$; $P = 0.022$), and galectin-3 ($r = -0.37$; $P = 0.0076$).

Conclusions: Asymptomatic heart involvement is common in SSc patients and includes focal and diffuse myocardial fibrosis. GDF-15 and galectin-3 were positively correlated with myocardial fibrosis parameters. Future outcome studies must show whether measurement of GDF-15 and galectin-3 in SSC patients might be may be useful in clinical practice.

1. Introduction

The presence of symptomatic heart involvement is recognized as a poor prognostic factor in patients with systemic sclerosis (SSc) [1]. The European Scleroderma Trials and Research group database confirmed low prevalence of severe heart disease but also confirmed its prognostic implications and impact on survival with 26% of deaths attributed to the cardiac involvement [2,3]. Typical heart damage in SSc is represented by a myocardial fibrosis, which is not consistent with large coronary artery distribution, and is a result of repeated ischemia - reperfusion abnormalities [4,5].

Through new and more refined imaging modalities like cardiovascular magnetic resonance (CMR) we might be able better recognize subclinical heart disease and hopefully gain new insight into long term prognosis in SSc patients. Compared with echocardiography, CMR appears to provide additional information by visualizing myocardial fibrosis and inflammation. T2-weighted techniques, e.g. assessment of gadolinium late enhancement (LGE) and assessment of myocardial

Abbreviations: CMR, cardiovascular magnetic resonance; DLCO, diffusing capacity of the lung for carbon monoxide; GDF-16, growth differential factor 15; GLP, global longitudinal peak systolic strain; LGE, late gadolinium enhancement; PIIINP, procolagen III N Terminal Propeptide.

* Corresponding author at: Department of Internal Medicine II, Faculty of Medicine in Pilsen, Charles University, Edvarda Beneše 13, 305 99 Plzen, Czech Republic.
E-mail address: seidlerovaji@fnplzen.cz (J. Seidlerová).

[1] The first two authors contributed equally to the manuscript.

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edema, are helpful in detection of localized fibrosis. However, diffuse fibrosis corresponds more accurately to the early (subclinical) stages of SSc [6]. T1-mapping technique was confirmed as promising method in recent studies [7]. The main benefits of T1-mapping technique are pixel-based parametric imaging and a possibility to quantify the T1 relaxation with premise to assess severity of involvement [7,8].

Numerous biomarkers have been shown to be associated with SSc activity or severity [9]. In our paper, we focused on those laboratory markers which emerged as promising surrogates for cardiac involvement in SSc patients. N-terminal pro-brain natriuretic peptide (NT-pro BNP) correlated with mean arterial pulmonary pressure and its measurement together with echocardiography and pulmonary function test increased sensitivity for diagnosing pulmonary hypertension. It also appeared to be a reliable predictor of mortality in SSc patients [9–11]. The other promising markers are cardiac troponins. Cardiac troponins measured by hypersensitive assays might be used for stratification of SSc patients, especially to identify those at risk of pulmonary hypertension [12]. Growth differential factor 15 (GDF-15) was correlated with SSc disease activity, especially with lung involvement [13] and with disease extent (limited vs. diffuse cutaneous SSc) [14]. Galectin-3, a predictor of heart failure development, was also shown to be a promising marker of SSc activity [15]. Procolagen III N Terminal Propeptide (PIIINP) is an aminopropeptide released during the synthesis of type III collagen. In SSc patients, it was reported that the levels of PIIINP were increased in both serum and bronchoalveolar lavage fluid and were related to the total skin scores and survival [16]. Interleukin-6 was shown to be associated with left ventricle diastolic dysfunction in SSc patients [17].

The aim of our study was to evaluate potential benefits of CMR parameters reflecting localized and diffuse myocardial fibrosis with respect to novel promising laboratory markers of cardiac involvement in SSc. These analyses might help to find clinically feasible algorithms for early detection of cardiac involvement in SSc patients.

2. Methods

2.1. Study population

This prospective study included patients with progressive systemic sclerosis, as defined by American College of Rheumatology [18], who were diagnosed and treated by rheumatology department of University hospital in Pilsen between January and June 2015. The exclusion criteria were as follows: 1) history of heart disease; 2) echocardiographic signs of pulmonary hypertension [19]; 3) other heart rhythm than sinus rhythm; 4) contraindication for CMR including gadolinium allergy; 5) glomerular filtration <30 ml/min; 6) pregnancy or breast feeding.

The control group included healthy volunteers who fulfilled the same exclusion criteria as SSC patients. This study was approved by Ethical committee of University hospital in Pilsen. All participants were acquainted with purpose and condition of the study and gave their informed consent. All study procedures were performed in the same day and in the same order: 1) blood sample taking; 2) CMR; 3) echocardiography.

2.2. Laboratory assessment

Serum creatinine, urinary albumin, myoglobin, uric acid, C reactive protein (CRP), NT-pro BNP were determined using original analytical kits from Roche on Cobas 8000 analyzer. High-sensitivity cardiac troponin I (hsTnI) was measured using the Architect i2000 platform with STAT High Sensitive Troponin-I assay (Abbott Diagnostics, USA). Circulating immune complexes (CIK) were measured by polyethylene glycole precipitation with photometric detection on Microplate Reader, in-house prepared reagents. Interleukin 6 (IL 6) was determined by enzyme immunoassay with chemiluminescent detection on Immulite 2000 analyser, Siemens. Anti-nuclear antibodies (ANA IgG) were assessed by indirect immunofluorescence test with HEp-2 cells, Euroimmun by fluorescence microscope, Olympus. Extractable Nuclear Antigens (ENA) were determined by enzyme immunoassay with fluorescent detection on Unicap 250 analyzer, Thermo Scientific. Complement component 3 and 4 (C3, C4) were measured by nephelometric immunoassay on BN II analyser, Siemens.

GDF-15 (RayBiotech, Norcross, USA), procolagen III N Terminal propeptide (Blue Gene, Shanghai, China), IL1R (Blue Gene, Shanghai, China) and galectin-3 (MyBiosource.com, San Diego, USA) concentrations were determined by ELISA kits on Nexgen ELISA four reader (Adaltis, Rome, Italy).

2.3. Echocardiography

Two-dimensional, M-mode and Doppler echocardiograms were acquired using an ultrasound system (Vivid 7, GE Medical Systems, Horton, Norway) with a 3.4-MHz multifrequency transducer. Primary measurements of mitral inflow included the peak early filling (E-wave) and late diastolic filling (A-wave) velocities, the E/A ratio, deceleration time (DT) of early filling velocity, which were derived by placing the cursor of the pulsed wave Doppler in the LV, above the tips of the mitral valve, to display the onset of mitral inflow, using a 5 MHz transducer. The passive LV filling (E′-wave) was measured from the pulsed wave tissue Doppler of the mitral septal annular velocity. Right ventricular systolic pressure was based on measurement of maximal tricuspid regurgitation velocity and applying the modified Bernoulli equation before addition of the estimated right atrial pressure. For assessment of the longitudinal speckle-tracking strain of the left ventricle, standard 2D ultrasound images at the parasternal mid-ventricular short-axis view (at the level of the papillary muscles) and from the apical long-axis, and two- and four-chamber views with a frame rate between 60 and 80 fps were recorded and stored digitally for offline analysis (EchoPac PC, GE Vingmed, Horton, Norway) [20,21].

2.4. Cardiovascular magnetic resonance protocol

CMR was performed using 3.0 T device (MAGNETOM Skyra, Siemens Healthcare, Erlangen, Germany) with an 32-element surface coil for thorax or body coil. Patients and volunteers were instructed to hold their breath in light inspiration during sequences acquisition. The sequences were synchronized with ECG. The protocol consisted in following order of 1) routine TrueFISP (True Fast Imaging with Steady-state Precession) sequence for morphological orientation and left ventricular function assessment in standard long-axis orientations (four-chamber and two-chamber); 2) the T2-weighted STIR (short Tau inversion recovery) sequence for detection of myocardial edema; 3) pre-contrast (native) T1 maps; 4) dynamic (first-pass) perfusion; 5) TrueFISP sequence covering whole left ventricle in short axis for functional analysis; 6) T1-weighted phase-sensitive inversion recovery (PSIR) sequence for detection of late gadolinium enhancement (LGE) and 7) post-contrast T1-maps. Native and post-contrast T1 maps were performed in three short-axis levels (basal, mid-ventricular and apical) of the left ventricle. The sequence based on modified look-locker inversion recovery (MOLLI) with single shot TrueFISP was part of commercially available package MyoMaps (Siemens Healthcare, Erlangen, Germany) [22]. T1 maps sequences were performed in the same levels using a single shot inversion recovery TrueFISP (fast imaging with steady-state free precession) with following parameters: TR 280.56 ms, TE 1.12 ms, echo spacing 2.7 ms, flip angle 35°, SL 8 mm, FOV 360 mm, matrix size 256 × 66%, voxel size 1.4 × 1.4 × 8 mm3, iPAT 2. The native T1 maps were performed using MOLLI type 5(3)3 sequence or. Post-contrast T1-maps used MOLLI type 4(1)3(1) sequences and were performed with minimal 15 min delay after contrast agent that was (Gadovist; Schering, Berlin, Germany) was administered intravenously at 0.05 mmol/kg body weight [22].

2.5. CMR analyses

All measurements were done by two independent radiologists (in random order) blinded to any previous results. Interobserver agreement of T1 values calculations was excellent (0.94). T1-values analysis was performed using dedicated software cvi42® (Circle Cardiovascular Imaging Inc., Calgary, Canada), the region of interest (ROI) was manually drawn in intramyocardial part of the interventricular septum and final T1 value was calculated as mean of values from all three layers (basal, mid-ventricular and apical). ROIs were carefully performed and the borders of the myocardium were excluded (exclusion surrounding tissue or the blood pool) [6,23]. Also regions of LGE were avoided to prevent influence of the final T1 value. Myocardial edema and LGE were visually assessed. The value of extracellular volume (ECV, %) fraction uses native and post-contrast myocardial T1 values and hematocrit were calculated according to following formula: [ECV (%) = (1 − hematocrit) × (1 / post-contrast T1 of myocardium − 1 / native T1 of myocardium) / 1 / post-contrast T1 of blood − 1 / native T1 of blood).

2.6. Assessment of SSc disease severity

The severity of skin fibrosis was quantified using the modified Rodnan skin score (mRSS), a measure of SSc disease severity and activity based on skin thickness at 17 anatomical sites. The skin thickness in each anatomical site is classified from 0 to 3, the maximum score beeing 51. It was shown that mRSS correlates with disease activity and prognosis [24].

Diffusing capacity of the lung for carbon monoxide (DLCO) was measured using a single breath method by means of body plethysmograph Platinum elite™ (Medgraphic, Saint Paul, MN, USA).

2.7. Statistical analysis

For statistical analysis, SAS software version 9.4 (SAS Institute Inc., USA) was used. The results are presented as arithmetic mean ± standard deviation, median with inter-quartile range (IQR) or as a proportion (percentage). Differences among the groups were assessed using the paired Student's *t*-test, the Kruskal-Wallis test and the χ^2 test, respectively. We also analysed data using Pearson correlation coefficient. To analyse independent relation between biomarkers under study and CMR parameters, we also used multivariate

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