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

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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.

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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

linear regression. As covariates we used parameters known to influence serum biomarkers levels.

3. Results

3.1. Characteristics of the study population

The present study included 33 SSc patients and 20 controls. There were more women in SSc patients than in control group (87.9 vs. 50.0%; P = 0.0024). Otherwise the two groups were similar in respect to age (mean 55.5 [SD 12.5] years), blood pressure (137.0/81.8 mm Hg), body mass index (27.2 [SD 5.0] kg/m^2), and presence of comorbidities (P for all ≥0.11). None of study subjects had history of atrial fibrillation. Median duration of SSc disease was 10 years (range 1–40). Majority of patients (87.9%) had diffuse form of SSc. Modiffied Rodnan skin score accounted 17.4 (SD, 4.4) points. Two thirds and one half of SSc patients used corticosteroids and disease-modifying anti-rheumatic drugs (DMARDs), respectively. As expected, laboratory parameters reflecting disease activity were higher in SSc patients compared to controls; erythrocyte sedimantion rate (10.0 [interquartile range, 7.0–14.0] vs. 6.0 [IQR, 4.0–8.5] mm/h; P = 0.0068); C reactive protein (4.6 [SD, 6.7] vs. 2.2 [SD, 1.6] mg/l; P = 0.063; extractable nuclear antigens (9.8 [IQR, 1.0–22.0] vs. 0.15 [IQR, 0.10–0,20] mm/h; P < 0.0001). Seven patients (21.2%) had diagnosed SSc associated interstitial lung disease; 48.5% of patients had pathological value of DLCO (<80%).

3.2. Echocardiography

Echocardiographic findings are presented in Table 1 and Supplement Table 1. There were no differences between SSc patients and controls with respect to conventional echocardiography parameters. On the other hand, the mean global peak systolic strain (GLPS) value was significantly lower in SSc patients compared to controls (18.6 ± 1.6 vs. 21.1 ± 1.2%; P < 0.0001). This was true for systolic strain measured in all views (Table 1). Moreover, GLPS was 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).

Table 1
Echocardiography and cardiac magnetic resonance.

	SSc n = 33	Controls n = 20	P
Echocardiography			
GLPS, (%)	18.6 ± 1.6	21.1 ± 1.2	<0.0001
APLAX, (%)	18.7 ± 1.7	20.7 ± 1.4	<0.0001
4CH, (%)	18.4 ± 1.9	21.4 ± 2.3	<0.0001
2CH, (%)	18.7 ± 1.5	21.0 ± 1.0	<0.0001
Magnetic resonance			
Late gadolinium enhancement, n (%)	14 (42.4)	0	0.0007
Extracellular volume, %	27.5 ± 2.8	22.8 ± 1.9	<0.0001
Native T1, ms	1258.9 ± 51.2	1192.2 ± 32.6	<0.0001
Post-contrast T1, ms	586.7 ± 64.3	629.3 ± 28.1	0.0018
Myocardial edema, n (%)	1 (3.0)	0	0.43
LV EF, %	57.3 ± 10.8	61.1 ± 5.2	0.16
Left ventricle mass, g	97.5 ± 22.5	120.8 ± 40.2	0.029
LV EDV indexed, ml/m^2	77 ± 18	67 ± 20	0.051
LV ESV indexed, ml/m^2	33 ± 6	26 ± 9	0.18
RV EDV indexed, ml/m^2	88 ± 25	82 ± 23	0.13
RV ESV indexed, ml/m^2	38 ± 9	29 ± 8	0.09
RV EF, %	57 ± 9	65 ± 8	0.12

Values are mean ± standard deviation or numbers (percentage).
P for difference between groups was calculated using Student *t*-test and χ^2 test, respectively.
LV EF - left ventricular ejection fraction; RV EF - right ventricular ejection fraction; LA - left atrium; GLPS - Global longitudinal peak systolic strain; APLAX - apical long axis view; 4CH - apical four chamber view; 2CH - apical two chamber view.
LV EDV – left ventricle end-diastolic volume; LV ESV – left ventricle end-systolic volume; RV – right ventricle.

3.3. Cardiac magnetic resonance

Supplement Fig. 1 provides images showing focal fibrosis assessed using LGE (panel A), non-contrast T1 maps (panel B and C) and demonstration of T1 value measurement (panel D). As expected SSc patients had higher prevalence of LGE presence compared to controls (42.4% vs. 0%; P = 0007), as shown in Table 1. All LGE lesions were small focal areas with non-ischemic pattern localized in intra-myocardial layer. Two thirds of the LGE lesions were situated in a free wall and rest in a septum. Using T2 STIR sequence we found small area of myocardial edema in one SSc patient (3.0%). ECV and native T1 relaxation time were significantly higher (P < 0.0001 for both), while post-contrast T1 was lower in SSc patients compared to controls (P = 0.0018; Table 1).

In further step, we analysed which factors might be associated with higher native T1 and ECV. First, we analysed these CMR parameters with respect to presence of focal fibrosis (LGE). Fourteen SSc patients with LGE had higher both ECV (28.8 ± 2.3 vs. 26.6 ± 2.7%; P = 0.021) and native T1 (1283 ± 49 vs. 1241 ± 46%; P = 0.020) compared to 19 SSc patients without LGE. These two CMR parameters were also significantly different between SSc patients without LGE and controls (P ≤ 0.019). Second, we investigated whether duration of disease might be associated with these CMR parameters. We did not find significant association between duration of disease and presence of LGE (P = 0.43), ECV (P = 0.47), pre-contrast T1 (P = 0.74), and post-contrast T1 (P = 0.81). Third, we tested possible influence of corticosteroid therapy on these CMR parameters. All CMR parameters under study were similar in patients treated with corticosteroids (n = 22) compared to corticosteroids naïve patients (n = 11, P ≥ 0.45).

3.4. Biochemical parameters

Serum concentration of high sensitivity troponin I and procollagen factor III were similar in the two groups (Table 2). On the other hand, concentrations of NT-pro BNP, GDF 15 and galectin-3 were significantly higher in SSc patients compared to controls (P ≥ 0.028; Table 2). Moreover, GDF 15 was also positively correlated with extracellular volume (r = 0.36; P = 0.0076; Fig. 1, panel A) and native T1 (r = 0.31; P = 0.023; Fig. 1, panel B). Post-contrast T1 did not correlate with GDF 15 (r = −0.08; P = 0.57). After adjustment for sex, age and renal function, GDF-15 remained significantly associated with extracellular volume (F = 8.27; P = 0.0060), native T1 (F = 5.46; P = 0.024) and GLPS (F = 8.08; P = 0.0066).

In SSC patients we observed that plasma level of GDF 15 was negatively correlated with diffusing capacity of the lung for carbon monoxide (r = −0.58; P = 0.0004; Fig. 2, panel A). Furthermore, plasma level of GDF 15 also positively correlated with modified Rodnan skin score (r = 0.59; P = 0.0003; Fig. 2, panel B). In multivariate analysis, GDF-15 remained significant determinant of DLCO (F = 18.53; P = 0.0002) and mRSS (F = 18.76; P = 0.0002).

CMR fibrosis parameters were also correlated with serum galectin-3 levels, ECV (r = 0.38; P = 0.0081; Fig. 1, panel C) and native T1 (r = 0.35; P = 0.012; Fig. 1, panel D). Post-contrast T1 did not correlate

Table 2
Biochemical data.

	SSc n = 33	Controls n = 20	P
hsTnI, ng/l	3.7 (2.3–9.2)	8.0 (2.9–13.9)	0.16
NT-proBNP, ng/l	127 (98–174)	47 (33 − 123)	0.0041
GDF 15, ng/ml	1.24 ± 0.51	0.81 ± 0.43	0.0027
Galectin-3, ng/ml	5.1 ± 8.8	1.5 ± 0.9	0.028
PIIINP, pg/ml	437.8 ± 648.3	240.8 ± 108.6	0.097

Values are mean ± standard deviation or numbers (percentage). P for difference between groups were calculated using Student *t*-test and χ^2 test, respectively. hsTnI, high sensitivity troponin I; GDF 15, growth differential factor 15; PIIINP, procolagen III N terminal propeptide.

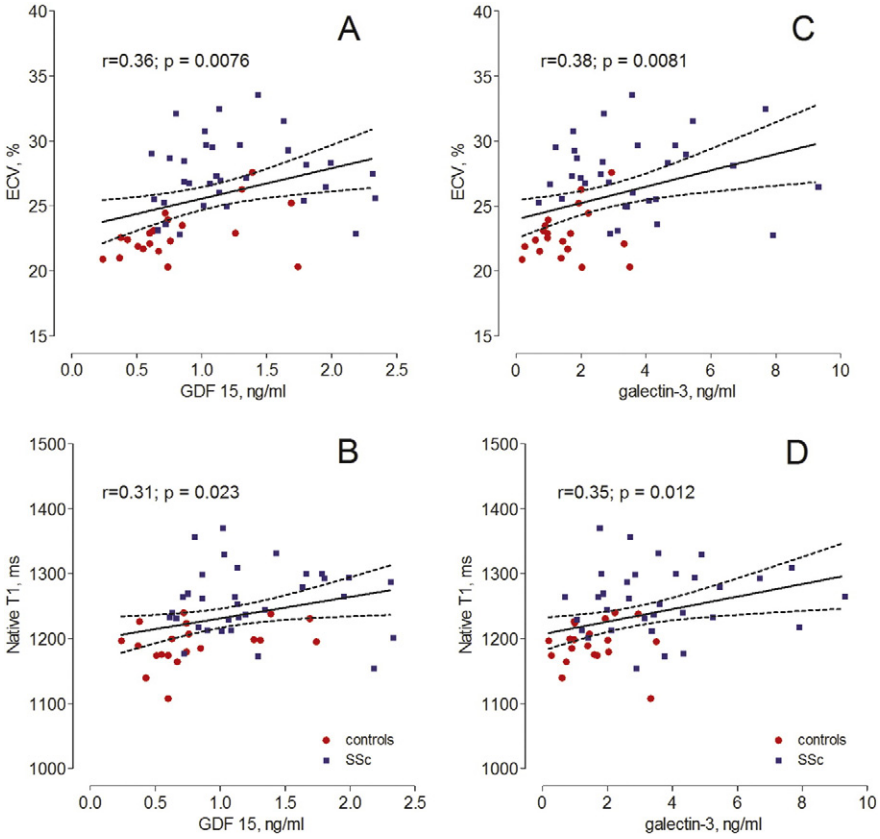

Fig. 1. GDF 15 and galectin-3 and their relation to CMR: extracellular volume and native T1.

with galectin-3 ($r = -0.23$; $P = 0.11$). Galectin-3 was also inversely correlated with GLPS ($r = -0.31$; $P = 0.023$). After adjustment for sex, age and renal function, galectin remained significantly associated with ECV ($F = 6.99$; $P = 0.011$) and native T1 ($F = 5.76$; $P = 0.020$) and GLPS ($F = 5.27$; $P = 0.026$). However, galectin-3 was not related to mRSS ($r = 0.31$; $P = 0.0.83$) and DLCO ($r = -0.17$; $P = 0.36$). GDF-15 and galectin-3 were closely inter-correlated ($r = 0.36$; $P = 0.0081$).

None of other laboratory parameters was related to CMR parameters under study. However, we observed inverse correlation between GLPS and IL-6 ($r = -0.30$; $P = 0.031$). Neither hsTnI nor NT-proBNP was related to GLPS ($P \geq 0.080$).

4. Discussion

Advantage of our study compared to previously published data lies in its comprehensive assessment of relation between novel CMR imaging and laboratory parameters. To our knowledge, no previous study addressed this issue. We observed that SSc patient had higher diffuse fibrosis parameters detected by CMR than controls. Moreover, we observed that CMR parameters of diffuse fibrosis correlated with growth differential factor 15 and galectin-3. GDF-15 was originally identified as a factor secreted by activated macrophages [25]. GDF-15 is especially well known for his role in the immune system and in the regulation of connective tissue metabolism. Lambrecht et al. reported that in SSc patients, serum GDF-15 levels were related to lung function impairment [13]. In line with this finding, we observed that circulating levels of GDF-15 were higher in patients with reduced DLCO (<0.75%) compared to SSc patients with preserved DLCO (1.15 ± 0.60 vs. 0.92 ± 0.22; $P = 0.042$).

Moreover, in our study circulating levels of GDF-15 correlated with severity of skin sclerosis. Similar findings were reported by Yanaba et al. [14]. The authors observed that serum GDF-15 levels were related with the extent of skin sclerosis and the severity of pulmonary fibrosis. Lambrecht et al. [13] demonstrated that GDF-15 expression and secretion are a direct consequence of fibrosis development and may contribute to underlying disease mechanisms, especially to the inflammatory stages of the fibrotic process. However, we did not find any association between GDF-15 and inflammatory markers (e.g. ESR and interleukin 6).

Zhou et al. showed that in patients with rheumatic heart disease those with atrial fibrillation had higher degree of cardiac fibrosis and plasma GDF-15 level and mRNA tissue level compared to those with sinus rhythm [26]. However, up to now no one demonstrated an association between GDF-15 and myocardial involvement in SSc patients. Meadows et al. [27] reported that GDF-15 levels were higher in SSc patients with systemic sclerosis-associated pulmonary arterial hypertension compared to SSc patients without pulmonary hypertension. GDF-15 levels also correlated positively with estimated right ventricular systolic pressure on echocardiography and plasma levels of the amino terminal propeptide form of brain natriuretic peptide. In our study, all SSc patients had estimated systolic pressure in main pulmonary artery lower than 35 mm Hg and no signs of pulmonary hypertension.

As regards to galectin-3, it was also related to CMR fibrosis parameters and global longitudinal peak systolic strain. Unlike GDF-15, galectin-3 was not related to pulmonary function or severity of skin fibrosis. In SSc patients, galectin-3 was associated with disease activity. Experimental studies suggested that galectin-3 might be an important mediator of cardiac fibrosis. It was also associated with incident heart failure and mortality in community [28]. All participants in our study had normal value of galectin 3 as defined by McCullough [29]. This finding might be interpreted as absence of subclinical heart failure.

The gradual development of diffuse myocardial fibrosis represents a major risk for SSc patient. In addition to the development of diastolic and systolic dysfunction, myocardial fibrosis might also increase risk

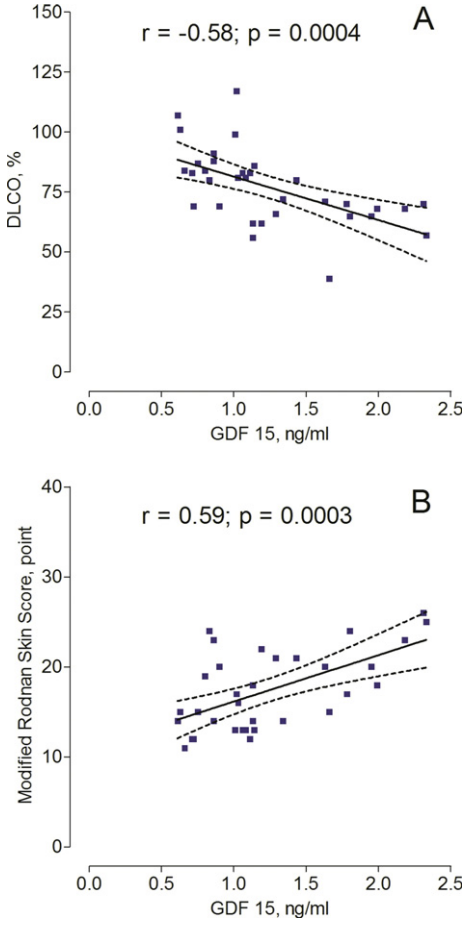

Fig. 2. GDF 15 and its relation to lung function (panel A) and modified Rodnan Skin Score (panel B) in SSc patients.

for development of arrhythmias or sudden death. Cardiac arrhythmias are associated with poor outcome in this disease [30]. Microvascular alterations with subsequent morphological vascular damage, collagen deposition and complex immune disturbances, are also thought to be involved in the pathogenesis of myocardial fibrosis [4,5,31].

The only non-invasive method enabling to assess focal myocardial involvement in ischemic and non-ischemic diseases is CMR. The detection of LGE corresponds, in non-acute involvement, to chronic fibrotic transformation of myocardial tissue [32]. Evaluation of diffuse involvement using established inversion recovery sequences requires comparison with remote and healthy muscle tissue which is problematic in systemic diseases [33]. In general, LGE evaluation is a suboptimal and not recommended for evaluation of diffuse myocardial involvement [8,34]. The T1 mapping is more suitable method and has been repeatedly used for this purpose, also in patients with systemic sclerosis [35]. We used comprehensive CMR protocol including pre and post-contrast T1 mapping a ECV calculation [36].

Until recently, the only possibility how non-invasively assess myocardial fibrosis was use of late gadolinium enhancement. However this technique is suitable for detection of focal fibrotic areas only. Moreover LGE allows only extent evaluation without possibility of parametric assessment [13]. On the other hand, T1 mapping allows precise quantification of diffuse changes in relaxation times affected by various involvements and is recently considered as a useful and effective method for detection and quantification of myocardial fibrosis in SSc patients [12]. In our study, we confirmed significant difference in native T1 mapping and ECV values between SSc patients and healthy controls. Moreover, we found focal myocardial edema only in one SSc patient. This observation increases the possibility that raised ECV and T1 value observed in SSc patients was caused by expansion of the myocardial collagen volume. Moreover, elevated levels of C reactive protein were found only in five SSc patients (in whom we did not detected myocardial edema). This finding further support hypothesis that observed changes were not caused by the local myocardial inflammation. These results are consistent with results of previously published studies focused on changes in the myocardium in SSc patients [7,8]. As measurement of ECV and T1 is relatively novel method, we still do not have data whether we should target our therapy according these parameters.

Global longitudinal peak systolic strain is a sensitive marker for detection of clinical and subclinical myocardial left heart dysfunction in a variety of pathologies. In our study, SSc patients with preserved left ventricle ejection fraction had impaired global longitudinal peak systolic strain compared to a matched control group. This is in line with report by Spethmann [37]. We also observed weak inverse association between GLPS and GDF-15 ($r = -0.31$; $P = 0.022$), galectin-3 (-0.31; $P = 0.023$), and interleukin-6 ($r = -0.30$; $P = 0.031$). Last-mentioned finding is in accordance with paper by Jurisic et al. [17].

The present study must be interpreted within the context of its limitations. First, it is a single-centre study with only a small number of patients. However, other studies in SSC patients using T1-mapping were performed in a comparable number of subjects [6,8]. Second, patient and control groups were not adequately matched in terms of sex difference. However, adjustment for sex did not change our results and sensitivity analysis performed in women only revealed results which were in the same direction as in the whole study population. Third, up to now we do not know prognostic value of novel CMR parameters. Fourth, in this report we show only cross-sectional data. However, we plan to report prospective data in future.

5. Conclusions

SSc patients had higher ECV and native T1 values. With these CMR fibrosis parameters correlated global longitudinal peak systolic strain and degree of skin involvement. From tested biochemical parameters, only GDF 15 and galectin-3 levels were associated with diffuse myocardial fibrosis detected by CMR. GDF-15 also correlated with severity of skin sclerosis and impaired pulmonary function in SSc patients. Whether measurement of GDF-15 and galectin-3 could be useful for risk stratification of SSc patients must be tested in future clinical outcome studies.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2017.08.072.

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Declaration of interest

The authors report no declarations of interest.

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