# Detection of myocardial inflammation by 18F-FDG-PET/CT in patients with systemic sclerosis without cardiac symptoms: a pilot study

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**Key words**: systemic sclerosis, heart involvement, FDG-PET/CT, strain echocardiography, myocardial inflammation

Competing interests: none declared.

## ABSTRACT

**Objective.** *Primary cardiac manifestation is a common complication of systemic sclerosis (SSc) with poor prognosis. The aim of the current study was to detect potential myocardial inflammation present in asymptomatic SSc patients by 18F-FDG-PET/CT and to investigate its relationship with early signs of myocardial dysfunction as detected by 2D speckle tracking echocardiography (2DSTE).*

**Methods**. *Sixteen consecutive patients with SSc and 9 control patients without clinical evidence of cardiac involvement were enrolled in the study. On 18F-FDG-PET acquired images blood-pool normalised SUV ratio and heterogenity index (HI: standard deviation of SUV divided with mean SUV) were calculated. Within 24 hours all SSc patients underwent 2DSTE strain analysis.*

**Results**. *Eight of 16 SSc patients were found to be visually PET-positive and showed significantly higher myocardial 18F-FDG SUV ratio (1.78±0.74 vs. 0.98±0.03; p<0.05) and heterogenity index (0.13±0.02 vs. 0.05±0.02; p<0.001) as compared to the control group. FDG-PET/CT derived values did not differ significantly between visually PET-negative (8/16) and control patients (SUV ratio: 0.98±0.05 vs. 0.98±0.03; HI: 0.05±0.01 vs. 0.05±0.02). Global left ventricular longitudinal strain values did not differ significantly between PET-positive and negative patients (17.18±3.49% vs. 17.59±3.65%).*

**Conclusion.** *Myocardial inflammation, as a potential sign of early cardiac involvement can be detected by 18-FDG-PET/CT in a considerable percentage of systemic sclerosis patients presenting without cardiac symptoms.*

## Introduction

Systemic sclerosis (SSc) is a rare, chronic, progressive systemic connective tissue disease characterised by microvascular dysfunction, immune-mediated inflammation and fibrosis with multi organ involvement. Cardiac involvement is common for patients with SSc, both in diffuse (DcSSc) and limited cutaneous forms (LcSSC) of disease with an estimated clinical prevalence of 15-35% (1, 2). Cardiovascular disease in SSc may be direct (myocarditis, heart failure, coronary artery disease, valvular and pericardial disease, conduction disturbances) and indirect (pulmonary artery hypertension (PAH) and renal crisis). When heart involvement becomes clinically evident, it appears as a bad prognostic factor with a patient mortality rate of up to 70% at 5 years (3). In the majority of patients (up to 80%), however cardiovascular disease is subclinical (4, 5) for variable duration. Therefore preclinical identification and monitoring of cardiac involvement is pivotal for adequate early management of these patients.

Routine transthoracic echocardiography (TTE) is the first line modality of choice in assessment of cardiac involvement (6). Echocardiography deformation imaging, such as speckle-tracking echocardiography (STE) for measurement of strain and strain rate, have been developed for a more accurate depiction of regional contractility and early detection of myocardial dysfunction (7). Indeed several recent publications have verified the promising role of STE for early detection of myocardial dysfunction in SSc patients (8-11).

Although diffuse myocardial fibrosis remains the pathologic hallmark of direct myocardial involvement (12), the presence of inflammation is often found in

biopsies of SSc patients suggesting that cardiac inflammation may be more common than originally appreciated. Moreover, the fibrotic process may be secondary to chronic inflammation of the heart (13). 18F-fluorodeoxyglucose(FDG)-positron emission tomography/computed tomo-graphy (PET/CT) is a non-invasive molecular imaging technique that is highly sensitive in quantitative evaluation of metabolically active processes such as inflammation. 18-FDG-PET/CT is generally gaining significance in the detection and monitoring of cardiac inflammation and infection (14, 15). We hypothesised that 18F-FDG-PET/CT may also be positive in asymptomatic SSc patients with potential subclinical myocarditis.

The aim of the current study was to detect potential myocardial inflammation present in asymptomatic SSc patients by 18F-FDG-PET/CT. We also sought to investigate the relationship between pathological myocardial findings on 18F-FDG-PET/CT and clinical indices of SSc disease and early signs of myocardial dysfunction as detected by 2DSTE.

## Patients and methods

*Study population*

Sixteen consecutive patients affected with SSc but without overt cardiovascular involvement were enrolled in the current prospective study. Inclusion criteria for the SSc group were: 1) age>18 and <85 years; 2) a previous diagnosis of SSc according to the ACR EULAR guidelines for SSc classification (16). Exclusion criteria were: 1) inability to provide informed consent; 2) known history of coronary artery disease, electrocardiographic signs of myocardial ischaemia, left ventricular ejection fraction <55%, regional wall motion abnormalities, left ventricular hypertrophy, significant valvular heart disease, pericardial effusion, severe pulmonary hypertension (pulmonary artery systolic pressure >40Hgmm). To avoid unnecessary radiation exposure to healthy subjects, 9 persons (5 male, 4 female; age 46.55±18.05 years) who underwent FDG-PET/CT examination for various other diagnostic reasons were enrolled as controls. Control subjects did not have SSc, nor had evidence of active inflammatory disease or cardiac disease, complied otherwise with the general exclusion criteria, and underwent the same FDG-PET/CT image acquisition and analysis protocol as the study patients. All subjects gave informed consent. The study was approved by the Local Ethical Committee for Clinical Research at the University of Szeged (ref. no.: 3647).

*Laboratory and clinical assessment*

All SSc patients underwent comprehensive rheumatologic and cardiovascular evaluation including, but not limited to, the assessment of: disease duration, EUSTAR disease activity score (17), Framingham score (18), presence of gastrointestinal involvement, pulmonary involvement, digital ulcers, prior immunosuppressive treatment, cardiovascular risk factors and current medication. General laboratory workup including determination of disease specific autoantibodies and markers of inflammation were performed according to local practice guidelines. Creatinine-kinase (CK) as a marker of gross skeletal muscle/myocardial injury was also ascertained (Table I).

*18F-FDG-PET/CT image acquisition protocol*

To suppress physiological glucose uptake in the myocardium patients were instructed to take low-carbohydrate, high-fat, high-protein diet for 24 hours followed by a minimum of 6 hours fasting before PET/CT scan examinations according to previously published cardiac FDG-PET/CT guidelines (19). A mean activity of 481.98±80.95 MBq (6,5 MBq/kg) FDG was administered intravenously. Blood glucose levels were checked (<8 mmol/L) beforehand. All scans were performed on an integrated whole-body PET/CT system (GE Discovery ST 4, GE Healthcare, Amersham, UK). Imaging of the cardiac region in 2D, non-gated mode was carried out 60 minutes after the administration of the radioisotope. PET scan data collection was completed by low-dose CT (120 kV and 70 mAs) acquisition. After imaging of the cardiac region, a routine whole-body acquisition was performed in 3-dimensional mode, extending from the skull base to the upper third of the thighs. Images were reconstructed using a standard ordered subset expectation maximisation algorithm with CT for attenuation correction.

*18F-FDG-PET/CT image analysis protocol*

FDG-PET images were visually evaluated for the presence of FDG uptake in the heart by consensus reading of two experienced PET/CT specialists. Based on uptake, FDG-PET images were classified into 4 patterns: "none," "diffuse," "focal," and "focal on diffuse." Quantitative evaluation of FDG uptake was performed by PMOD version 3.704 software (PMOD Technologies Zurich) on attenuation corrected 2D PET images. Reorientation of axial cardiac images was performed. Seventeen segments cardiac model was used according to the scientific statement from the American Heart Association (20). Body weight standardised uptake value (SUV) in g/ml was calculated. Definition of left ventricular volume of interest (VOI) was performed in a semi-automated fashion. Blood pool VOI was contoured in the left ventricular cavity. Mean global, segmental myocardial and blood pool SUV were calculated. To avoid misinterpretation due to differing patient metabolic characteristics, SUV values were divided by blood pool SUV to create normalised SUV ratios (21). To further specify pathophysiological uptake a coefficient of variation as a metric of image heterogenity was also determined. Average and standard deviation of SUV values were calculated from SUV values in the 17 myocardial segments. The coefficient of variation (heterogenity index; HI) was calculated as the standard deviation of SUV divided by the average of SUV (22). Widespread diffuse myocardial FDG uptake exceeding liver uptake was considered as failed inhibition of physiological myocardial glucose uptake and patients were excluded from further analysis (23).

*Echocardiography*

All patients with SSc underwent comprehensive echocardiography within 24

**Table I**. Clinical characteristics of systemic sclerosis patients.

| | All SSc patients n=16 | DcSSc n=8 | LcSSc n=8 |
|---|---|---|---|
| Age (year) | 59 ± (44-74) | 62 ± (45-74) | 57± (44-62) |
| Sex (male/female) | 2 M/14 F | 1M/7F | 1 M/7 F |
| Disease duration (years) | 5.56 ± 6.22 | 5.38 ± 6.56 | 5.75 ± 5.43 |
| EUSTAR disease activity score | 2.88 ± 1.77 | 3.75 ± 1.35 | 2 ± 1.38 |
| Framingham score | 2.81 ± 3 | 2.83 ± 2.25 | 2.79 ± 3.76 |
| ANA positive (n) | 11 | 5 | 6 |
| ACA positive (n)* | 6 | 0 | 6 |
| anti-Scl70 positive (n) | 4 | 4 | 0 |
| DLCO (%) | 49 ± 22 | 46 ± 27 | 52 ± 18 |
| Pulmonary involvement (n) | 10 | 6 | 4 |
| Digital ulcers (n) | 8 | 2 | 6 |
| Gastrointestinal involvement (n) | 13 | 7 | 6 |
| Hypertension (n) | 7 | 4 | 3 |
| Hyperlipidaemia (n) | 7 | 4 | 3 |
| Diabetes (n) | 3 | 1 | 2 |
| Immunosuppressive treatment in the past (n) | 8 | 6 | 2 |
| Immunosuppressive treatment in the last 6 months (n) | 4 | 4 | 0 |
| Corticosteroid (up to 4 mg/day) treatment at the time of PET/CT examination (n) | 3 | 3 | 0 |
| Beta-blockers (n) | 4 | 3 | 1 |
| ACE-inhibitors/ARB (n) | 5 | 4 | 1 |
| Calcium Channel Inhibitors (n) | 6 | 3 | 3 |
| Statins (n) | 5 | 3 | 2 |
| Platelet aggregation inhibitor (n) | 6 | 2 | 4 |
| CK, U/l | 99 ± 54.65 | 105.25 ± 63.96 | 86.5 ± 33.07 |
| CRP, mg/L | 19.40 ± 29.68 | 23.31 ± 39.08 | 15.50 ± 18.07 |
| ESR, mm/h | 28.10 ± 15.53 | 31.87 ± 15.44 | 24.32 ± 15.67 |
| WBC, G/L | 8.40 ± 2.10 | 8.85 ± 2.44 | 7.94 ± 1.75 |

ACA: anti-centromere antibody; ACE: angiotensin converting enzyme; ANA: antinuclear antibodies; anti-Scl70: anti-topoisomerase; ARB: angiotensin II receptor blocker; CK: creatinine-kinase; CRP: C-reactive protein; DLCO: diffusing capacity of the lung for carbon monoxide; DcSSc: diffuse cutaneous systemic sclerosis; ESR: erythrocyte sedimentation rate; LcSSc: limited cutaneous systemic sclerosis; WBC: white blood cell count. *$p<0.05$.

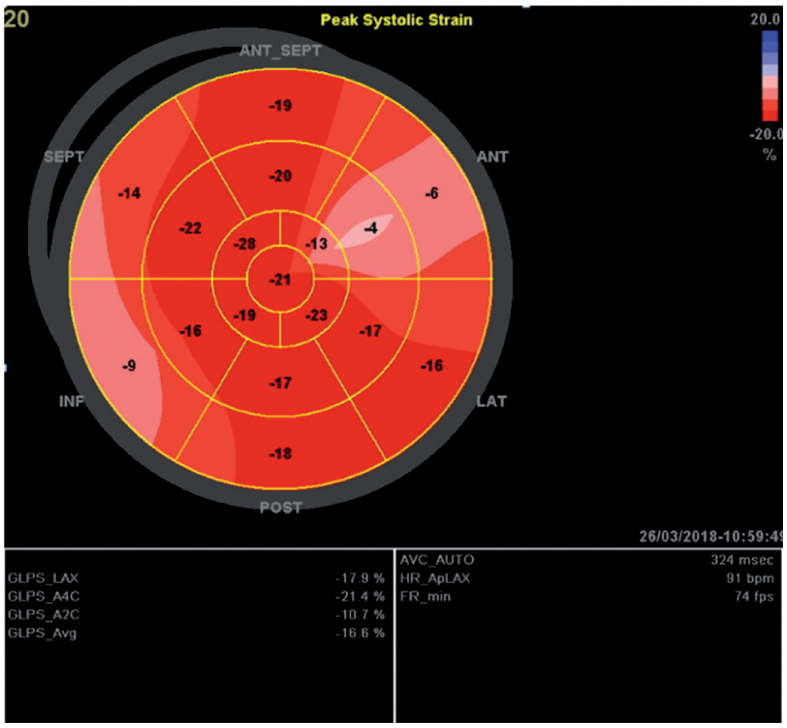


**Fig. 1.** Longitudinal strain bull's eye plot derived from two-dimensional speckle tracking in patient with systemic sclerosis. Decreased strain values in inferior and anterior segments.

hours after PET/ CT scanning. Echocardiographic examinations were performed in all patients at rest using commercially available ultrasound machine (Vivid S70, GE Medical Systems, Horten, Norway). Left ventricular (LV) end-diastolic and end-systolic diameters, interventricular septum diastolic (IVS), and posterior wall thickness (PW), left atrial (LA) volumes, maximum LA size measurements were performed. Early (E) and late (A) mitral inflow velocity, E/A ratio, and deceleration time were obtained. Systolic (S'), early diastolic (E'), and late diastolic (A') velocities were also measured by tissue Doppler imaging (TDI). Pulmonary artery systolic pressure was estimated (24). All measurements were performed according to the recommendations of the European Association of Cardiovascular Imaging/American Society of Echocardiography (25). 2D speckle tracking echocardiography (2DSTE) analyses were performed on standard echocardiographic grey-scale images. The loops were recorded with a frame rate between 60 and 80 frames per second. LV longitudinal strain was determined from the 3 apical (2-, 3-, and 4-chamber) views. The 2D images were analysed using dedicated software package (EchoPac PC, version, GE Vingmed, Horton, Norway). During analysis, the endocardial border was manually traced at end systole, and the region of interest width was adjusted to include the entire myocardium. The software then automatically tracks and accepts segments of good tracking quality and rejects poorly tracked segments while allowing the observer to manually override its decisions on the basis of visual assessments of tracking quality. Peak longitudinal strain values were determined in 17 segments by Bull's eye method (Fig. 1). Based on a guideline published by the American Society of Echocardiography and a meta-analysis of normal values, global longitudinal systolic peak strain (GLPS) values below 19.7% were considered pathological (25, 26).

*Statistical analysis*

Data are presented as mean ± standard deviation (SD) unless otherwise stated. Comparisons between FDG-PET/

CT positive and negative, DcSSc and LcSSc patients were performed using Student's *t* tests or by non-parametric Mann-Whitney U-test, as appropriate. Comparisons between categorical variables were made with the Fisher's exact test. All tests were two-sided and *p*-values <0.05 were considered statistically significant. Overall and segmental agreement between FDG-PET/CT and 2DSTE was assessed using Cohen's kappa coefficients. Correlations between the two methods were tested by Pearson or Spearman's correlation tests, as appropriate. All analyses were performed using JMPV.14 statistical software v.14 (SAS Institute Inc., Cary, NC, USA).

## Results

Clinical characteristics of the SSc patient population are presented in Table I. Of the 16 patients 8 patients presented with limited cutaneous and 8 with diffuse cutaneous form of systemic sclerosis. Clinically expected differences between the two subgroups were related to a more frequent need for immunosuppressive and low-dose corticosteroid therapy in the DcSSc group, and the differences between autoantibody positivity, although statistically significant difference was observed only with regard to anti-centromere antibody-positivity.

### *FDG-PET/CT*

Dietary protocol to suppress normal glucose uptake was followed in all 16 SSc patients and 9 control subjects. Low carbohydrate, high-fat, high-protein diet time was: 32.5±3.14 hours, while total fasting time direct before image acquisition was: 18.32±4.74 hours. Blood glucose levels before radiopharmaceutical administration were 4.92±0.99 mmol/l. According to visual classification of cardiac FDG-PET images in SSc patients, 8/16 none, 0/16 diffuse, 6/16 focal, 2/16 focal on diffuse patterns were found. In all of the control subjects, the cardiac FDG-uptake was near or equal to lower than blood pool activity meaning a "none" pattern (Fig. 2). In SSc patients, global myocardial SUV was 3.019±0.02 g/ml and blood pool SUV was 2.1±0.56 g/ml. In control patients, the same values were 1.81±0.26 g/ml and 1.85±0.27 g/ml ($p<0.05$). Normalisation according to blood pool uptake SUV ratio in the patient population was 1.38±0.65 and 0.98±0.03 in the control group ($p<0.05$). Heterogenity indices of SSc and control patients were 0.095±0.04 and 0.05±0.02 ($p<0.05$). Of the 16 SSc patients 8 visually "PET positive" (focal or focal on diffuse myocardial FDG uptake) patients showed significantly increased normalised SUV ratio (1.78±0.74 versus 0.98±0.03, $p<0.05$) and a significantly higher heterogenity index (0.13±0.02 *vs*. 0.05±0.02, $p<0.001$) as compared to the control group (Fig. 3). In contrast, in the 8 visually "PET-negative" SSc patients, normalised SUV ratio and heterogenity index did not differ significantly from control subjects (normalised SUV ratio: 0.98±0.05 *vs*. 0.98±0.03; HI: 0.05±0.01 *vs*. 0.05±0.02). No significant differ-

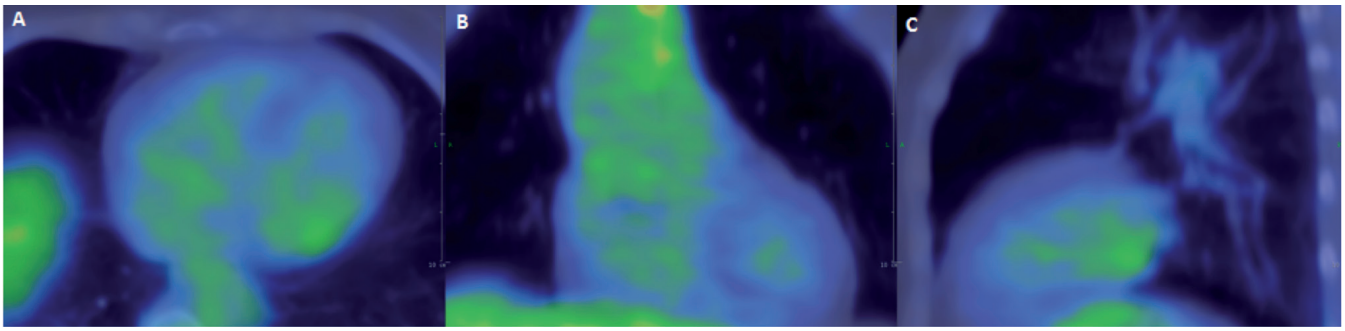


**Fig. 2.** FDG-PET/CT examination of a control patient without known cardiovascular disease. FDG-PET/CT fused axial (**A**), coronal (**B**) and sagittal (**C**) slices. The images show successful dietary suppression of physiological myocardial glucose uptake with no focal or diffuse increased uptake. Global normalised standard uptake ratio: 0.97, heterogenity index: 0.03.

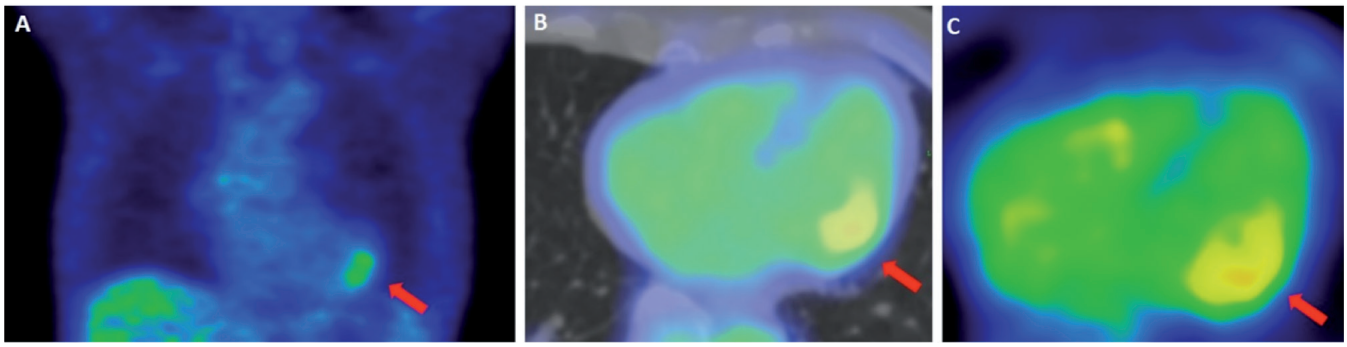


**Fig. 3.** FDG/PET-CT examination of a PET-positive systemic sclerosis patient presenting without clinical signs of primary cardiac involvement. **A**: Coronal FDG-PET image of chest. **B**: Axial FDG-PET/CT fused image of the heart. **C**: Same level axial FDG-PET slice without CT fusion. PET images show increased focal FDG uptake (arrows) in the lateral wall in the presence of otherwise suppressed myocardial glucose uptake. Global normalised SUV ratio: 1.10, heterogenity index: 0.14.

ences were detected between the two groups in regards to clinical characteristics and laboratory parameters (Table II). No correlations were found between FDG-PET/CT derived values and type of SSc, disease activity scores, disease duration and laboratory indices of inflammation or cardiac involvement and echocardiographic parameters.

*Echocardiography*

Due to poor acoustic window, comprehensive transthoracic echocardiography, global and segmental strain measurements were unsuccessful in 1 of 16 SSc patients. Echocardiography characteristics of the SSc patient population are presented in Table III. There were no significant differences between DcSSc and LcSSc patients based on TTE parameters. There was also no statistically significant difference between PET positive and negative groups in regards to conventional TTE findings and, of special interest, global longitudinal peak strain (17.18±3.49 *vs*. 17.59±3.65). No correlations were found between GLPS values and FDG-PET/CT derived indices (global SUV, normalised global SUV and HI).

*Spatial agreement*

Spatial agreement between FDG-PET/CT and 2DSTE derived segmental longitudinal strain was assessed according to the 17- segment model in a total of 234 left ventricular segments. Overall, 96/234 segments with increased FDG-uptake were found. According to 2DSTE analysis 48/234 segments had pathological low segmental longitudinal strain value. Overall and PET positive patient spatial agreement between the two methods was poor (κ=0.04 and κ=0.021). To avoid possible orientation bias for further analysis, the left ventricular bull's eye was divided into four anatomical regions: apex (13-17 segments), septum (2-3, 8-9 segments), anterior and anterolateral wall (1,6,7,12 segments) and inferior and inferolateral wall (4,5,10,11 segments). Pathological FDG-PET/CT (20/56) and STE derived segmental longitudinal strain (21/56) regions were determined. Overall and in patients with pathological PET findings, spatial agreement between the two methods remained to be poor (κ=0.12 and κ=0.15).

**Table II.** Clinical characteristics of PET positive and PET negative systemic sclerosis patients.

| | PET positive n=8 | PET negative n=8 |
|---|---|---|
| Age (year) | 58 (44-74) | 61 (55-67) |
| Sex (Male/Female) | 0 M/ 8 F | 2 M/ 6 F |
| Disease duration (years) | 7.65 ± 6.96 | 3.5 ± 4.95 |
| EUSTAR disease activity score | 2.75 ± 1.66 | 3 ± 1.96 |
| Framingham score | 2.13 ± 3.53 | 3.47 ± 3.53 |
| DcSSc (n) | 4 | 4 |
| LcSSc (n) | 4 | 4 |
| ANA positive (n) | 5 | 6 |
| ACA positive (n) | 4 | 2 |
| anti-Scl70 positive (n) | 0 | 4 |
| DLCO (%) | 53 ± 27 | 46 ± 16 |
| Pulmonary involvement (n) | 5 | 5 |
| Digital ulcers (n) | 4 | 4 |
| Gastrointestinal involvement (n) | 6 | 7 |
| Hypertension (n) | 3 | 4 |
| Hyperlipidaemia (n) | 4 | 3 |
| Diabetes (n) | 0 | 3 |
| Immunosuppressive treatment in the past (n) | 4 | 4 |
| Immunosuppressive treatment in the last 6 months (n) | 2 | 2 |
| Corticosteroid treatment (up to 4 mg/day) at the time PET/CT examination (n) | 0 | 3 |
| Beta-blockers (n) | 0 | 4 |
| ACE-inhibitors/ARB (n) | 2 | 3 |
| Calcium Channel Inhibitors (n) | 4 | 2 |
| Statins (n) | 2 | 3 |
| Platelet aggregation inhibitors (n) | 2 | 4 |
| CK U/l | 96.6 ± 65.09 | 100.71 ± 51.41 |
| CRP, mg/L | 22.43 ± 38.82 | 16.35 ± 18.98 |
| ESR, mm/h | 31.12 ± 18.60 | 25.8 ± 13.03 |
| WBC, G/L | 8.6 ± 1.47 | 8.2 ± 2.69 |
| EF (%) | 69.87 ± 5.59 | 65.12 ± 7.35 |
| GLPS (%) | 17.18 ± 3.49 | 17.59 ± 3.65 |

There were no statistically significant differences between PET positive and PET negative systemic sclerosis patients.
ACA: anti-centromere antibody; ACE: angiotensin converting enzyme; ANA: antinuclear antibodies; anti-Scl70: anti-topoisomerase; ARB: angiotensin II receptor blocker; CK: creatinine-kinase; CRP: C-reactive protein; DLCO: diffusing capacity of the lung for carbon monoxide; DcSSc: diffuse cutaneous systemic sclerosis; EF: ejection fraction; ESR: erythrocyte sedimentation rate; GLPS: global longitudinal peak systolic strain; LcSSc: limited cutaneous systemic sclerosis; WBC: white blood cell count.

## Discussion

To the best of our knowledge, this is the first study to investigate early stage myocardial involvement in SSc patients with FDG-PET/CT. We prospectively evaluated the myocardial glucose metabolic activity in SSc patients without clinical signs of primary cardiac involvement and compared it to normal control subjects. Major finding of our study is that pathological myocardial FDG uptake as a sign of inflammation can be found in a significant number of SSc patients with otherwise no clinical evidence of cardiovascular disease.

The pathological hallmark of cardiovascular involvement in SSc is patchy myocardial fibrosis reported in up to 80% of cases in autopsy studies (12). Pathways leading to this final stage of disease are multifactorial. Recurrent episodes of ischaemia-reperfusion injury provoked by microvascular dysfunction (27) and vasospasm of small coronary arterioles, play a significant role in the development of patchy "contraction band necrosis" leading to fibrosis. The inflammatory and autoimmune nature of SSc and association with skeletal myositis suggests that myocardial inflammation my also play a crucial role in the development heart disease in SSc. Historically, overt myocarditis had only been reported in isolated cases of SSc patients with acute and severe cardiac symptoms

Table III. Echocardiographic parameters of systemic sclerosis patients.

| | All SSc patients | DcSSc | LcSSc |
|---|---|---|---|
| LVEF (%) | 67.5 ± 6.77 | 66.5 ± 7.96 | 68.5 ± 5.70 |
| LV EDD (mm) | 46.06 ± 3.02 | 45.63 ± 3.15 | 46.5 ± 3.02 |
| LV IVS (mm) | 9.62 ± 1.08 | 10.13 ± 0.83 | 9.12 ± 1.12 |
| LV PW (mm) | 9.56 ± 1.31 | 10.00 ± 1.41 | 9.12 ± 1.12 |
| LA V (ml) | 59.88 ± 20.25 | 56.54 ± 21.78 | 63.22 ± 19.45 |
| E/A | 0.91 ± 0.39 | 0.89 ± 0.41 | 0.92 ± 0.40 |
| E/E' | 10.57 ± 3.97 | 12.54 ± 4.93 | 8.89 ± 2.03 |
| TAPSE (mm) | 22.86 ± 4.71 | 22.00 ± 5.03 | 23.62 ± 4.62 |
| PASP (Hgmm) | 28.3 ± 6.40 | 34.67 ± 3.51 | 25.57 ± 5.38 |
| GLPS (%) | 17.37 ± 3.44 | 15.61 ± 3.97 | 18.91 ± 2.10 |

There were no statistically significant differences between DcSSc and LcSSc patient groups.
A: late mitral inflow velocity; DcSSc: diffuse cutaneous systemic sclerosis; E: early mitral inflow velocity; E': early diastolic velocity; EDD: end diastolic diameter; EF: ejection fraction; GLPS: global longitudinal peak systolic strain; LA V: left atrial volume; LcSSc: limited cutaneous systemic sclerosis, LV: left ventricular; IVS: intraventricular septum; PASP: pulmonary artery systolic pressure; PW: posterior wall; TAPSE: tricuspid annular plane systolic excursion.

(28-30). More recently however, in an endomyocardial biopsy study of 25 SSc patients presenting with clinical signs of cardiac involvement at least low grade inflammation was diagnosed in almost all of the patients and high grade myocardial inflammation was present in 20 % of the cases (31). This was confirmed by Pieroni *et al*. (32) who in an even larger cohort of SSc patients with newly developed symptoms of heart failure and cardiac involvement proved myocarditis to be a common finding. Due to the poor prognosis of clinically manifest cardiovascular disease in SSc, early detection of myocardial involvement has become a crucial aspect of patient management. Screening imaging modalities to identify early myocardial involvement have concentrated on the detection of fibrosis and/or consequential myocardial dysfunction (33, 34). More recently, advances in magnetic resonance imaging (MRI) technology have allowed an early detection of surrogate parameters of inflammation, indicative of myocardial inflammatory processes. Indeed MRI has proven to be a useful tool to detect myocardial inflammation in several forms of rheumatic disorders: rheumatoid arthritis (35), systemic lupus erythematosus (SLE) (36), ankylosing spondylitis (37), ANCA-associated vasculitis (38). However, MRI has its limitations, which are particularly apparent in chronic myocarditis with diagnostic accuracy as low as 50% (39).

Increased glucose metabolism due to high glycolytic activity of inflammatory cells (monocyte, macrophage, lymphocyte) is considered a hallmark of inflammation. Thus PET using 18F-FDG is the standard reference for molecular imaging of myocardial inflammation (40). At the present time FDG-PET/CT is already clinically established in the diagnosis and follow up of cardiac sarcoidosis (41). It is also gaining acceptance in the detection and monitoring myocarditis in general (42). 18F-FDG PET has shown showed excellent agreement with endomyocardial biopsy for detecting active inflammatory foci in subjects with clinically suspected active acute myocarditis (43). 18F-FDG PET may also provide useful information in addition to cardiac magnetic resonance (CMR) to distinguish between acute and chronic myocardial inflammation (44, 45). Potential feasibility of PET scan with 18F-FDG to detect and monitor active cardiac involvement and treatment efficacy in patients with systemic sclerosis has been reported in one case (46). In the current study we report the presence of myocardial inflammation detected by FDG-PET/CT in SSc patients without cardiac symptoms. These findings are in agreement with previous reports based on CMR imaging (47, 48). Our results are also similar to those of Perel-Winkler *et al*. who detected myocardial inflammation by 18F-FDG-PET-CT not only in symptomatic but also in asymptomatic SLE patients (49). PET positive patients were identified by increased FDG uptake paired with heterogeneous distribution according to the pathophisology of disease presentation by "patchy" immune-inflammatory foci (50). PET positive patients exhibited significantly higher FDG uptake and heterogeneity index as compared to both FDG negative and control patients. Incidence of subclinical myocardial inflammation of 50% was comparable to one CMR based investigation (53%) (47), and significantly higher than in another 10% (48). However, authors in the later study acknowledged that the low incidence reported by them was probably due to the lack of T1, T2 mapping and extracellular volume assessment (48).

Although the relatively low number of patients prevented conclusive comparisons between PET-positive and -negative SSc patients, some differences are apparent. It is somewhat unexpected that all the anti-Scl70-positive patients had negative PET-CT results, although this antibody is known to be associated with a higher risk of cardiopulmonary parenchymal organ involvement. It coincides with the finding that all 3 patients who were taking moderate dose of methylprednisolone (up to 4 mg) clustered in the PET-negative subgroup. These 3 patients were also anti-Scl70 positive, and even this low dose of corticosteroid therapy may have had an impact on the myocardial inflammatory process. Underlining the subclinical nature of disease presentation, no significant differences between laboratory indices of inflammation or myocardial necrosis were identified between PET positive and negative patients similarly to several other studies (10, 47, 48). There was also no significant difference between PET positive and negative patients in regards to disease activity, disease duration or disease type (DcSSc *vs*. LcSSc). We note that the primary aim of our work was to evaluate whether it is feasible to detect early myocardium involvement in SSc by FDG-PET/CT. The study population was thus selected with a relatively strict exclusion of cardiovascular factors unrelated to SSc but otherwise represented an unselected and heterogeneous group with regard to SSc clinical manifestations. Validation of clinical correlations is out of the scope of this work and requires further studies.

Echocardiography is an essential, first line, noninvasive method to detect cardiac involvement in patients with SSc. Common pathological findings in overt disease may include wall motion disturbances, reduced ejection fraction, pericardial effusion and PAH. Recently echocardiographic deformation imaging modalities such as STE strain analysis have been developed to provide more accurate depiction of regional contractility and dysfunction otherwise not seen with routine parameters. Several STE studies have described subclinical left ventricle (8), right ventricle (9) and left atrial dysfunction (10) in asymptomatic SSc patients as markers of early myocardial involvement. In the current study, we report decreased left ventricle GLPS values indicative of subtle myocardial dysfunction in asymptomatic SSc patients. These results are in accordance with previously published findings (8, 51). We found no significant differences in left ventricular GLPS values between PET positive and negative groups. Accordingly, no significant correlations were found between left ventricular GLPS values and the measures of pathological glucose uptake (normalised SUV ratio, HI). We also investigated spatial agreement between the two methods on segmental and regional basis as well. Our study demonstrated poor agreement of FDG-PET/CT and left ventricular strain in regards to spatial distribution of imaging findings. These differing results between FDG-PET/CT and 2D speckle tracking echocardiography strain analysis maybe explained by the two different phases of disease evolution is SSc. In myocardial biopsy studies inflammatory infiltrates were recognisable as a form of early phase immune modulated interstitial/perivascular inflammation which may ultimately lead to the second phase of disease, replacement fibrosis (13, 30). The results capture the dual nature of the disease: pathological glucose uptake representing early immune mediated inflammation and lower strain values representing subtle mechanical changes caused by fibrosis. Distinct differences between the two imaging modalities should also be noted in regards to clinical implementation. Echocardiography is a validated, readily available noninvasive screening tool to detect and follow myocardial involvement in patients with systemic sclerosis. On the other hand, routine clinical use of FDG-PET-CT is not recommended at this time and before possible clinical implementation further investigations are warranted to evaluate specificity, sensitivity and overall clinical impact (prognostic value, therapeutic relevance) of the method in asymptomatic SSC patients. Until then we suggest that asymptomatic FDG-positive patients should be followed more closely with currently validated cardiac techniques (*i.e.* CMR).

*Limitations of the study*

Some limitations of the study should be noted. First: the sample size was small due to the pilot nature of the study and the rare incidence of SSc. Additionally, we excluded patients with overt cardiac symptoms, already diagnosed cardiovascular disease further narrowing the patient population pool. Second: the study lacks a true comparator for myocardial inflammation as detected by FDG-PET/CT. Standard of reference or lack thereof is a common problem when evaluating imaging modalities for myocarditis. Endomyocardial biopsy (EMB) is still considered the gold standard for diagnosing myocarditis. However, it is not frequently performed due to risk, cost, variable specificity, and lack of experience in some facilities (42). EMB in the current, asymptomatic patient population was not considered because of its invasive nature and potential risks. In the recent decades CMR has gained wide acceptance both as a research tool and as a clinical diagnostic method in myocarditis. Although CMR is the most validated imaging method of myocarditis it still is not considered to be gold standard. In one study for example it was non-decisive or falsely negative in half of patients with biopsy-proven myocarditis (52). Nonetheless CMR should be considered as first choice comparator in future studies. Furthermore, possible simultaneous assessment of cardiac inflammation and fibrosis using an integrated FDG-PET/MR examination would be particularly well suited for comparative studies. Initial experiences with this hybrid method to detect myocardial involvement in cardiac sarcoidosis (53) and in suspected myocarditis (23) have been promising. Third: pathological 18-FDG detected by FDG-PET/CT is highly sensitive, but nonspecific method for visualisation of inflammation. Due to lack of standardisation in regards to patient preparation, reporting of images and – as mentioned above – a true comparator, false positive diagnosis is possible. Two patients in the current study exhibiting "focal on moderately elevated" diffuse uptake could potentially also be interpreted as false positive due to unsuccessful physiologic glucose uptake suppression. Fourth: concomitant corticosteroid therapy at the time of FDG-PET/CT examination therapy, even in low doses, may mask potential underlying low-grade myocardial inflammation, potentially leading to false negative results. Fifth: the study lacks a matched, healthy control population for 2DSTE imaging. Limitations of 2DSTE analysis include intervendor and patient-specific clinical factor variability. Strain values are influenced by age, concomitant cardiovascular risk factors, haemodynamic values, and medication. Thus, the definition of normal strain values remains problematic (54). Nonetheless a guide on normal values by the American Society of Echocardiography and previously published meta-analysis of normal ranges in healthy subjects allow for a meaningful interpretation of our results (25, 26).

## Conclusion

Myocardial inflammation, as a potential sign of early cardiac involvement may be detected by 18-FDG-PET/CT in a considerable percentage of systemic sclerosis patients presenting without cardiac symptoms. We hypothesise that this imaging method has the potential to be used as a new diagnostic tool for the evaluation of SSc patients. However, it is evident that before clinical implementation further clinical investigations are warranted in larger patient groups to determine the prognostic impact of these findings and to identify specific patient risk groups in whom this examination may be of direct therapeutic relevance.

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