Troponin I and echocardiography in patients with systemic sclerosis and matched population controls

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Objectives: Cardiac manifestations in systemic sclerosis (SSc) are associated with poor prognosis. Few studies have investigated cardiac troponins in SSc. We studied the relationships between echocardiographic abnormalities, cardiac biomarkers, and disease manifestations in a population-based cohort of patients with SSc and controls.

Method: The study comprised 110 patients with SSc and 105 age- and sex-matched population-based controls. We examined ventricular function, heart valves, and estimated pulmonary arterial pressure (ePAP) by echocardiography in all participants. Disease characteristics, manifest ischaemic heart disease (IHD), and measurements of N-terminal prohormone brain natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin I (hs-cTnI) were tabulated.

Results: NT-proBNP and hs-cTnI levels were higher in SSc patients than controls. Both NT-proBNP and hs-cTnI were associated with the presence of echocardiographic abnormalities. Forty-four SSc patients and 23 control subjects had abnormal echocardiograms (p = 0.002). As a group, SSc patients had lower (but normal) left ventricular ejection fraction (LVEF, p = 0.02), more regional hypokinesia (p = 0.02), and more valve regurgitations (p = 0.01) than controls. Thirteen patients and four controls had manifest IHD. Decreased right ventricular (RV) function (n = 7) and elevated ePAP (n = 15) were exclusively detected among SSc patients.

Conclusions: Both NT-proBNP and hs-cTnI were associated with echocardiographic abnormalities, which were more prevalent in SSc patients than in controls. Our results thus suggest that hs-cTnI could be a potential cardiac biomarker in SSc. Low RV function and signs of pulmonary hypertension (PH) were uniquely found in the SSc group. SSc patients had more valve regurgitation than controls, an observation that warrants more clinical attention.

Systemic sclerosis (SSc) is an autoimmune systemic disease involving a diversity of internal organs. The hallmarks of the disease are vasculopathy, extensive fibrosis, and autoantibody production. Focal myocardial fibrosis, as described by Bulkley et al in 1976 (1), progresses silently while clinical symptoms such as arrhythmias, left and right heart dysfunction, or cardiac death may manifest suddenly without warning (2). The occurrence of cardiac manifestations in SSc is associated with poor prognosis (3) and international guidelines recommend yearly echocardiographic screening to detect pulmonary hypertension (PH) and/or cardiac abnormalities (4). Echocardiography has been used in SSc since the 1980s but, with few exceptions (5–8), previous studies have been small or performed on selected patient groups.

Biomarkers such as N-terminal prohormone brain natriuretic peptide (NT-proBNP) and cardiac troponin (cTn) have more recently been used to identify subjects at risk of cardiovascular disease in the general population (9, 10). NT-proBNP is mainly produced by ventricular myocytes under haemodynamic stressful conditions. NT-proBNP levels are used to monitor heart failure (9) and have been studied extensively in SSc, where they have emerged as a biomarker to monitor pulmonary arterial hypertension (PAH) (11). cTn has a high specificity for myocardial tissue and is the preferred biomarker to diagnose myocardial necrosis/infarction. Recently, high-sensitivity (hs) immunoassays for cTn have become available. These can detect low levels of circulating troponins, which may be released in other conditions than acute ischaemic heart disease (10).

Both cardiac troponin T (cTnT) and cardiac troponin I (cTnI) are widely used today, and elevated levels of both predict unfavourable long-term outcomes (10). Because of the elevated levels of cTnT in patients with muscular or renal disease even in the absence of cardiac...
manifestations, cTnI has been suggested as a better marker of cardiac disease in patients with these conditions (12). Uric acid (UA) is the final oxidation product of purine metabolism. Elevated levels occur in conditions with impaired oxidation such as chronic heart failure (13) and PH (14) and are associated with poor prognosis (15), but whether they can be used for screening is still under investigation. We compared echocardiographic findings in a population-based group of SSc patients and matched controls. Additionally, we investigated the associations between echocardiographic abnormalities, clinical characteristics, and circulating levels of NT-proBNP, hs-cTnI, and UA.

Method

Patients and controls

All participants were > 18 years old and recruited from the adult population in Stockholm County between August 2006 and December 2009 (n = 1 534 272). During this period we identified 149 prevalent cases who fulfilled the American College of Rheumatology (ACR) criteria for SSc (16). We asked all 149 SSc patients if they wanted to participate in this study and 110 patients (74%) gave their consent. We recruited 105 control subjects from the same population. These were identified through use of the national registration number (includes date of birth and is coded for gender) and matched to the patients for age, gender, and region of living.

All participants underwent a thorough medical examination at the Department of Rheumatology, Karolinska University Hospital. The echocardiograms were performed at the Department of Clinical Physiology, Karolinska University Hospital or at Aleris Fysiologlab, Sophiahemmet. All were investigated for previous cardiovascular disease (CVD), traditional CVD risk factors, biomarkers of systemic inflammation, and autoantibody patterns. Carotid ultrasound and electrocardiograms were performed. These data have been described previously (17, 18).

Skin thickness was measured by the modified Rodnan skin score (mRSS) (19). Patients were classified as limited cutaneous SSc (lcSSc) or diffuse cutaneous SSc (dcSSc) (20). Organ involvement was defined as follows:

- Pulmonary fibrosis: signs of fibrosis on X-ray or high-resolution computed tomography (HRCT)
- PAH: a resting mean pulmonary artery pressure (PAP) ≥ 25 mmHg with a pulmonary capillary wedge pressure of ≤ 15 mmHg measured at right heart catheterization
- Myositis: muscular weakness and elevated creatine kinase (CK) and signs of inflammation on magnetic resonance imaging (MRI), electromyography, or muscular biopsy
- Kidney disease: a history of scleroderma renal crisis (SRC) (21)
- Ischaemic heart disease (IHD): myocardial infarction (MI) [confirmed by electrocardiography and a reversible rise in plasma CK muscle–brain fraction (CK-MB) or troponin T] or angina pectoris (confirmed by an exercise stress test).

The local ethics committee of Karolinska University Hospital approved the study and all participants gave their written informed consent.

Echocardiography

Echocardiography was performed either with an Acuson Sequoia ultrasound system (Acuson, Mountain View, CA, USA) with a 2.5- or 3.5-MHz transducer or with a GE Vingmed ultrasound system (Vivid 7; Horten, Norway). The results were interpreted by a single experienced reader, blinded to patient or control status and without knowledge of other test results. The patients and controls were investigated in random order. Two-dimensional measures were taken as recommended by the American Society of Echocardiography (22). Measures of wall thickness and left ventricle diameter are given as the mean of two measurements. Global left ventricular (LV) function was assessed with visual estimation of LV ejection fraction (LVEF) (23) and by measuring atrioventricular plane displacement (24). The valves were studied carefully for valve thickening and other malformations. Doppler and colour Doppler were used to assess valvular stenosis and/or leakage. Regurgitations were graded from the spectral Doppler intensity, the width of the colour jet at the base, and the appearance of the colour Doppler jet. Regurgitation was graded from 1 to 4, where 1 is mild and 4 severe, and considered present if it was grade 1 or more. Valvular abnormalities were classified as either abnormal localized echodensity adjacent to valve leaflets or valve thickening. PAP was estimated by continuous wave Doppler measurement of the peak systolic velocity of the tricuspid regurgitation. We used the following criteria for suspected PH:

1. Tricuspid regurgitation velocity > 2.9 m/s, corresponding to an estimated pulmonary artery pressure (ePAP) > 34 mmHg at rest with or without additional echocardiographic parameters suggesting PH such as a dilated right ventricle and impaired right ventricular (RV) function.
2. Tricuspid regurgitation velocity < 2.9 m/s but additional echocardiographic parameters suggesting PAH. In the absence of tricuspid regurgitation, PAP was considered normal.

RV function was considered abnormal if the tricuspid annular plane systolic excursion (TAPSE) of the RV free
wall was < 17 mm. Tissue Doppler measurements were made at the septal basal segment of the left ventricle and the systolic velocity and diastolic E and A wave velocities were measured.

Laboratory analyses
hs-cTnl (reagent 3P23) and UA (reagent 3P39-21) were measured with an Architect ci16200® Integrated System (Abbott Laboratories, Abbot Park, IL, USA). The limit of detection of the troponin I assay was 2 ng/L and the total coefficient of variation (CV) was 5.5% at 22 ng/L and 4.4% at 200 ng/L. The UA method had a total CV of 2.1% at 280 μmol/L and 0.7% at 580 μmol/L.

NT-proBNP was measured with a Roche cobas 8000 analyser, using the e602 module (Roche Diagnostics, Mannheim, Germany) according to the manufacturer’s specifications. The instrument had a total CV of 0.9% at 107 ng/L and 1.3% at 2060 ng/L.

Glomerular filtration rate (GFR) was estimated from cystatin C measurements. Cystatin C (reagent 1014, Gentian, Moss, Norway) was analysed on an Architect ci8200® analyser (Abbott Laboratories). The total analytical imprecision of the cystatin C method was 1.1% at 1.25 mg/L and 1.4% at 5.45 mg/L. The equation used for calculating GFR in mL/min/1.73 m² from the cystatin C results (raw data in mg/mL) was:

$$y = 79.901x^{-1.4389}$$

A line immunoassay (Euroline; Euroimmun, Lübeck, Germany) was used to detect immunoglobulin (Ig)G antibodies to scleroderma-70/anti-topoisomerase I (ATA), centromere proteins A and B (ACA), and RP11 and RP155 (subunits of RNA polymerase III; ARA) in serum.

Statistics
Continuous variables are presented as mean ± standard deviation or, when non-normally distributed, as median and interquartile range. Categorical variables are presented as proportions. Non-normally distributed variables were log transformed to achieve a normal distribution, when possible. Continuous variables were compared using an analysis of variance (ANOVA) or a t-test or, if a normal distribution was not achieved, the Mann–Whitney test. The χ² test or Fisher’s exact test was used to evaluate categorical variables, the latter when any cell contained five or fewer observations. As our primary aim was to describe patterns of associations for the investigated variables, we did not adjust for multiple comparisons.

Logistic regression models were used to estimate crude odds ratios (ORs) and 95% confidence intervals (CIs) for the association between echocardiographic findings and age and sex. Thereafter, multivariable logistic regression models, adjusted for age and sex, were performed to investigate the association between echocardiographic findings and disease characteristics and biomarkers.

Statistical analyses were performed using JMP software (SAS Institute, Cary, NC, USA). A p-value of < 0.05 was considered statistically significant.

Results
The SSc patients had a lower body mass index (BMI), diastolic blood pressure (BP), and eGFR, but higher triglyceride and NT-proBNP levels than the controls. The levels of inflammatory biomarkers and hs-cTnl were also higher in SSc patients, although the numerical absolute differences were fairly small. Levels of UA did not differ. All patients and 88% of the controls had detectable hs-cTnl levels (> 2 ng/L). A history of IHD was more common in patients than in controls; seven patients and three controls were diagnosed with MI and six patients and one control with angina pectoris. Although almost 50% of both patients and controls had ever smoked, only 11% of the patients and 7% of the controls were current smokers. Participant characteristics are presented in Table 1.

Echocardiographic findings in patients and controls
Overall, 44 SSc patients and 23 controls had abnormal echocardiograms. The patients had lower (but within normal range) LVEF, more often LVEF < 50% and/or LV hypokinesia than the controls. Of the 11 participants with LVEF ≤ 50%, seven SSc patients and the only control had a history of IHD.

The mitral E velocity/septal e velocity (the E/e’ ratio) was higher (but normal) in patients than in controls (p = 0.04), but signs of diastolic dysfunction (an E/e’ ratio > 13) did not differ between patients and controls (16 patients vs. 10 controls, p = 0.1).

Eight patients, but no controls, had TAPSE < 17 mm and/or large RV diameter and the patients had a lower TAPSE than the controls (p = 0.03).

Fifteen patients but no controls had a tricuspid insufficiency (TI) velocity > 2.9 m/s and the pressure difference between the right atrium and the right ventricle was greater in the patients than in the controls (p = 0.0001). Ten of the 15 patients with a TI velocity > 2.9 also had pulmonary fibrosis.

The patients had more valvular regurgitation than the controls (p = 0.04), especially when we included the three SSc patients who had been subject to valvular replacement due to regurgitation; two mitral and one aortic valve prosthesis (p = 0.01). One additional SSc patient was diagnosed with severe mitral regurgitation and subsequently had a valve replacement. The two controls with prostheses had aortic valve replacements due to stenosis.

Echocardiographic findings are reported in Table 2. The characteristics of the 44 patients with echocardiographic abnormalities are described in detail in Supplementary Table S1.
Factors associated with echocardiographic abnormalities in SSc patients

All variables presented in Table 1 were investigated for associations with the following four echocardiographic outcomes: (i) any echocardiographic abnormalities, (ii) ePAP > 34 mmHg, (iii) valvular regurgitation, and (iv) LVEF < 50% and/or LV hypokinesia. As these outcomes and investigated variables were often associated with age and sometimes with sex, we adjusted for age and sex in the multivariable analysis.

1. Any echocardiographic abnormality was associated with kidney disease, PAH, a low eGFR, inflammatory biomarkers, and higher levels of hs-cTnI, NT-proBNP, and UA.

2. ePAP was associated with pulmonary fibrosis, PAH, conduction defects, hs-cTnI and NT-proBNP, a low eGFR, and inflammatory biomarkers.

3. Valvular regurgitation was associated with kidney disease, PAH, and high levels of hs-cTnI and NT-proBNP. Notably, no patient with dcSSc or ATA had valvular regurgitation.

4. A low LVEF/LV hypokinesia was associated with kidney disease, higher levels of hs-cTnI and NT-proBNP, and conduction defects. There was also a trend towards association with IHD, as expected.

Associations between echocardiographic outcomes and clinical/laboratory variables in SSc patients are presented in Table 3.

Patient characteristics associated with cardiac biomarkers

All variables presented in Table 1 were investigated for associations with cTnI, NT-proBNP, and UA.
Patients with manifest IHD or PAH had higher hs-cTnI and NT-proBNP levels, but the levels of UA did not differ. Elevated hs-cTnI and NT-proBNP was also seen in patients with previous myositis but there was no association with present CK levels. Patients with kidney disease and/or a low eGFR had higher levels of hs-cTnI, NT-proBNP, and UA.

hs-cTnI was associated with elevated markers of inflammation while NT-proBNP was associated with a lower β-glucose level, lower BMI, and lower levels of low density lipoprotein (LDL). We did not find any association with smoking status. Levels of hs-cTnI and characteristics of the outliers are presented in Figure 1.

After adjusting for (a) kidney disease and (b) eGFR, NT-proBNP remained associated with all three echocardiographic outcomes (p < 0.05). Likewise, hs-cTnI was still associated with a higher ePaP (p < 0.0001) and LVEF < 50%/hypokinesia (p = 0.02) but not with valvular regurgitation.

Age- and sex-adjusted β-coefficients and p-values are presented in Table 4.

**Table 2. Echocardiographic findings in SSc patients and controls.**

| Echocardiographic findings      | SSc patients (n = 110) | Controls (n = 105) | p-value |
|---------------------------------|------------------------|--------------------|---------|
| LV dimension (mm)              | 45 ± 5                 | 45 ± 4             | ns      |
| Septal thickness (mm)          | 10 ± 2                 | 9 ± 2              | ns      |
| Posterior wall thickness (mm)  | 9 ± 1                  | 9 ± 1              | ns      |
| LV AV mean (mm)                | 12 ± 2                 | 13 ± 2             | 0.04    |
| LVEF %                         | 58 ± 7                 | 60 ± 4             | 0.02    |
| LVEF % ≤ 50 (n)                | 10                     | 1                  | 0.005   |
| Presence of regional LV hypokinesia (n) | 10                     | 2                  | 0.02    |
| Mitral E velocity (m/s)        | 0.8 ± 0.2              | 0.7 ± 0.2          | 0.03    |
| Mitral A velocity (m/s)        | 0.7 ± 0.2              | 0.7 ± 0.2          | ns      |
| Mitral E/A                     | 1.1 ± 0.3              | 1.1 ± 0.3          | ns      |
| Mitral E/e’ (septal e’)        | 9.8 ± 3.9              | 8.7 ± 3.4          | 0.04    |
| IVRT (ms)                      | 84 ± 19                | 85 ± 15            | ns      |
| Mitral E deceleration time (ms) | 206 ± 52               | 201 ± 51           | ns      |
| Any valvular abnormality (n)   | 27                     | 19                 | ns      |
| Valvular sclerosis             | 19                     | 16                 | ns      |
| Valve replacement (n)          | 3*                     | 2                  | ns      |
| Valvular regurgitation ≥ 2/4 (n) | 6                     | 1                  | 0.04    |
| Mitral valve regurgitation      | 2                      | 1                  | 0.03    |
| Tricuspid valve regurgitation   | 3                      | 0                  | 0.007   |
| Aortic valve regurgitation      | 1                      | 0                  | 0.06    |
| TAPSE (mm)                     | 22 ± 4                 | 23 ± 4             | ns      |
| TAPSE < 17 mm or large RV (n)  | 8                      | 0                  | ns      |
| Pulmonary acceleration time (m/s) | 105 ± 32              | 114 ± 35           | 0.01    |
| Measurable TI maximal velocity (n) | 73                    | 54                 | < 0.0001|
| TI velocity > 2.9 m/s or other signs of PH (n) | 15                     | 0                  | < 0.0001|
| Pressure difference between RV and RA (mmHg) | 28 ± 11               | 23 ± 4             | 0.0001  |
| Presence of pericardial effusion (n) | 2                     | 0                  | ns      |
| Any echocardiographic abnormality (n) | 44                    | 23                 | 0.002   |

SSc, Systemic sclerosis; AV, atrioventricular; LVEF, left ventricular ejection fraction; LV, left ventricle; RV, right ventricle; RA, right atrium; IVRT, isovolumic relaxation time; TAPSE, tricuspid annular plane systolic excursion; TI, tricuspid insufficiency; PH, pulmonary hypertension.

Bold numbers indicate significant p-values (p < 0.05).

* One additional patient had severe mitral regurgitation leading to valve replacement shortly after inclusion.

**Discussion**

Our results demonstrate that high circulating levels of hs-cTnI constitute, similar to NT-proBNP, a good biomarker of echocardiographic abnormalities in SSc.

Our study is the first to evaluate hs-cTnI in SSc patients but a few other studies have investigated other troponins. In 2006, Montagnana et al analysed cTnT in 40 female SSc patients and 40 controls and found no difference in troponin levels (25). Since then, high-sensitivity troponin assays have been introduced (10) and Avouac et al (8) recently reported that levels of hs-TnT are high in SSc and are correlated to cardiac involvement and PH. Vasta et al reported four SSc cases with elevated troponins and associated cardiac abnormalities (26). Pieroni et al examined seven patients with cardiac symptoms and mildly elevated troponin in a cohort of 181 patients and found evidence of myocarditis in all seven patients. Even more interesting is their observation that cTn levels declined after treatment with corticosteroids and cyclophosphamide (27).
### Table 3. Associations between echocardiographic outcomes and clinical/laboratory variables in SSc patients.

| Characteristics                  | Abnormal echocardiography (n = 44) | Estimated PAP > 34 mmHg (n = 15) | Valvular insufficiency (n = 9) | LVEF < 50% and/or LV hypokinesia (n = 12) |
|----------------------------------|------------------------------------|----------------------------------|-----------------------------|------------------------------------------|
| Age                              | 1 (1.06–1.7)***                    | 1.05 (1.00–1)*                   | 1.0 (1.03–1.0)**            | 1.03 (0.98–1.09)                        |
| Gender: female                   | 0.4 (0.1–1.1)                      | 0.35 (0.10–1.3)                  | 0.42 (0.10–2.17)            | 0.14 (0.04–0.54)**                      |
| Calculations below are adjusted for age and sex |
| Disease duration                 | 1.02 (0.95–1.1)                    | 1.0 (0.91–1.05)                  | 0.95 (0.97–1.09)            | 1.0 (0.9–1.06)                          |
| Subtype lcSSc                    | 0.48 (0.15–1.49)                   | 0.94 (0.24–4.8)                  | na (no dcSSc)*              | 1.6 (0.3–12.3)                         |
| Pulmonary fibrosis               | 2.18 (0.86–5.7)                    | 4.6 (13.19–17.7)*               | 0.45 (0.05–6.6)             | 1.9 (0.5–7.7)                          |
| PAH                              | 9.4 (1.4–189)*                     | 44.2 (7.8–345)****              | 9.04 (1.5–58.7)*            | 3.5 (0.4–24.3)                         |
| Myositis                         | 1.4 (0.3–6.9)                      | 1.03 (0.05–6.9)                  | 5.7 (0.2–80.6)              | 4.7 (0.9–20.8)                         |
| Kidney disease                   | 35 e9 (100–1)*                     | 9.1 (0.38–78.4)†                | 57.2 (3.9–1375.1)**         | 10.6 (1.01–97.2)**                     |
| Skin score                       | 1.0 (0.9–1.1)                      | 1.0 (0.89–1.13)                  | 1.0 (0.9–1.2)               | 1.1 (0.9–1.2)                          |
| ACA                              | 0.35 (0.12–0.99)*                  | 0.96 (0.23–3.52)                 | 2.2 (0.5–11.3)              | 0.70 (0.1–3.5)                         |
| ARA                              | 0.64 (0.21–1.8)                    | 0.54 (0.08–2.4)                  | na (no ARA)*                | 1.9 (0.5–6.8)                          |
| IHD                              | 4.7 (0.9–29.7)†                    | 1.3 (0.16–6.9)                   | 4.7 (0.7–31.2)              | 1.7 (0.2–10.0)                         |
| Ever smoked                      | 2.2 (0.5–9.5)                      | 0.8 (0.2–2.8)                    | 2.5 (0.5–15.0)              | 1.0 (0.08–21.7)†                       |
| BMI (kg/m²)                      | 1.8 (0.7–5.5)                      | 0.5 (1.09–1.2)                   | 0.9 (0.9–5.2)               | 1.3 (0.3–5.5)                          |
| Systolic BP (mmHg)               | 0.9 (0.9–1.01)                     | 0.9 (0.9–1.01)                   | 0.99 (0.92–1.02)            | 0.98 (0.53–1.02)                       |
| Diastolic BP (mmHg)              | 0.9 (0.9–1.02)                     | 0.98 (0.9–1.05)                  | 0.98 (0.9–1.05)             | 0.96 (0.3–1.04)                        |
| Cholesterol (mmol/L)             | 0.8 (0.5–1.3)                      | 1.2 (0.7–2.2)                    | 1.3 (0.6–2.7)               | 0.8 (0.4–1.6)                          |
| HDL (mmol/L)                     | 0.35 (0.1–1.7)                     | 0.6 (0.07–5.5)                   | 3.7 (0.36–61.0)             | 0.24 (0.01–2.9)                        |
| LDL (mmol/L)                     | 0.9 (0.6–1.6)                      | 1.5 (0.8–2.9)                    | 1.04 (0.5–2.3)              | 0.9 (0.5–1.9)                          |
| Triglycerides (mmol/L)           | 1.7 (0.6–4.7)                      | 0.7 (0.2–2.8)                    | 1.1 (0.2–5.1)               | 0.8 (0.1–3.7)                          |
| P-glucose (mmol/L)               | 5.8 (0.7–79.9)                     | 7.5 (0.7–77.8)                   | 0.69 (0.004–19)             | 1.9 (0.1–18.0)                         |
| Conduction defects               | 2.4 (0.7–9.2)                      | 4.0 (1.1–14.8)*                  | 0.8 (0.1–4.3)               | 6.1 (1.3–29.6)*                        |
| NT-proBNP (ng/L)                 | 25 (1.5–46)***                     | 1.9 (12–32)**                    | 2.4 (4.1–50)**              | 3.2 (1.8–71)**                        |
| hs-cTnI (ng/L)                   | 2.8 (1.3–6.4)**                    | 3.2 (2.4–8)**                    | 3.2 (1.1–10.6)**            | 3.8 (1.7–10.1)**                      |
| Uric acid (µmol/L)               | 1.01 (1.00–1.01)*                  | 1.00 (0.99–1.0)                  | 1.00 (0.99–1.01)            | 1.0 (0.99–1.00)                        |
| CK (ng/L)                        | 0.6 (0.3–1.02)                     | 0.69 (0.26–1.29)                 | 0.61 (0.1–1.5)              | 1.2 (0.5–2.1)                          |
| eGFR (mL/min/1.73 m²)            | 0.2 (0.03–0.49)***                 | 0.3 (0.1–0.8)**                  | 0.3 (0.1–1.3)               | 0.5 (0.2–1.5)                          |
| hsCRP (mg/L)                     | 1.7 (1.1–2.6)***                   | 1.8 (1.0–3.6)*                   | 0.55 (0.25–1.09)            | 1.07 (0.6–2.1)                         |
| ESR (mm/h)                       | 2.0 (1.1–3.3)***                   | 2.3 (1.8–6.1)*                   | 0.4 (0.2–1.1)               | 1.1 (0.5–2.8)                          |

**Ssc, Systemic sclerosis; PAP, pulmonary arterial pressure; LVEF, left ventricular ejection fraction; LV, left ventricular; lcSSc, limited cutaneous systemic sclerosis; na, not available; PAH, pulmonary arterial hypertension; ACA, anti-centromere antibodies; ATA, anti-topoisomerase 1 antibodies; ARA, anti-RNA polymerase 3 antibodies; IHD, ischaemic heart disease; BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NT-proBNP, N-terminal prohormone brain natriuretic peptide; hs-cTnI, high-sensitivity cardiac troponin I; CK, creatine kinase; eGFR, estimated glomerular filtration rate; hsCRP, high-sensitivity C-reactive protein; ESR, erythrocyte sedimentation rate.**

Values are given as odds ratio (95% confidence interval).

Bold numbers indicate significant p-values (p < 0.05).

* p < 0.05, ** p < 0.01, *** p < 0.001, **** p < 0.0001, † p = 0.06.
Impaired renal function is often associated with IHD (28). In our study, abnormal echocardiographic findings were associated with both kidney disease and a low eGFR, but the positive associations between echocardiographic findings and NT-proBNP and hs-cTn remained after adjustment for measures of renal disease/function. Thus, the high levels of these cardiac biomarkers cannot solely be explained by accumulation due to impaired renal clearance, a mechanism previously reported in other settings (29).

An increased prevalence of cardiac disease in SSc patients with myopathy has been reported previously (30) and we observed a higher hs-cTnI in patients with a history of myositis (p = 0.02), but there was no association between CK levels and hs-cTnI. The high levels of hs-cTnI found in SSc patients are thus likely to originate from the heart and not from skeletal muscles. Aggarwal et al reported similar observations in patients with polymyositis without cardiac involvement. They noted a positive association between high levels of CK and cTnT but no association between CK and hs-cTnI (31).

In line with the study by Avouac et al (8), we found an association between PAH and elevated hs-cTn, but in contrast we did not find any association between hs-cTn and traditional risk factors for cardiac disease. Instead we found an association between inflammatory parameters and elevated hs-cTn. This could imply an underlying inflammatory component to the findings of elevated cTn, such as myocarditis, but were not able to verify this in the present study. Myocarditis needs to be evaluated in larger studies or confirmed by MRI.

We consider it would be useful to evaluate hs-cTn as a potential biomarker for cardiac involvement in SSc. Whether hs-cTnI or hs-cTnT is preferable in SSc remains to be determined, a topic discussed recently by Hughes et al (32).

The small number of patients with a history of myositis or kidney disease in our study is a limitation and these findings should be confirmed in larger cohorts. However, we consider it is important to examine both renal and muscular disease/dysfunction in SSc patients in further studies to determine the specificity of cardiac troponins as measures of SSc-related cardiac disease.

In this population-based study, 40% of the SSc patients had one or more echocardiographic abnormalities. Both the left and right sides of the heart were affected. We also found that the patients had more valvular regurgitations than the controls, which in four of our cases had led to valvular prosthesis surgery. In autopsy studies only minor valve abnormalities have been reported (1, 33). However, autopsy records report morphological changes whereas valvular insufficiencies can also be found in heart valves with normal structure. Although there are several echocardiographic studies on SSc, there are only a few reports on valve regurgitations or stenosis. In one small study of 11 patients with progressive SSc, mitral valve prolapse was recorded in two patients (34). In 1990, Kazzam et al examined 30 patients and 30 controls and found mitral regurgitation in 67% of the SSc patients vs. 15% of the controls (35). Another study that compared SSc, myositis, and systemic lupus erythematosus (SLE) patients and controls...
reported that patients with SSc had the highest frequency of mitral and/or aortic regurgitation, with 10% vs. 1.7% in SLE and 0% among myositis patients and controls (36). In a large study comprising 570 SSc patients, 7.2% had mitral regurgitation and 2.4% aortic regurgitation (6). Taken together, our study provides further evidence that valve regurgitation is enhanced and should be specifically looked for in SSc, a fact that has not yet gained much attention.

In our study, impaired LV function was associated with male gender, conduction defects, and a history of kidney disease. There was also a trend towards an association with myositis and IHD. These observations are essentially similar to the large multicentre European League Against Rheumatism (EULAR) scleroderma trial and research (37) study of 7073 patients, although the contribution of man-

The decline in diastolic function has been the subject of numerous studies of SSc because of the assumption that it mirrors myocardial fibrosis. In our study, LV diastolic dysfunction was seen in only 15% of patients. The prevalence of diastolic dysfunction in SSc measured with conventional Doppler echocardiography has been higher in previous studies: 20–40% (5, 6, 39, 42). Several variables affect the assessment of diastolic function and studies use various definitions. Lee et al found that the measure used in this study, the E/e’ ratio, was more sensitive than the E/A ratio in SSc patients (43). We did not record any difference in diastolic dysfunction between patients and controls. Other studies have similar results, especially after adjusting for other predisposing factors such as heart rate, systolic dysfunction, and PH (44, 45).

In our study, RV abnormalities such as decreased RV function and/or large RV diameter and signs of PH were exclusively detected in SSc patients. Altogether, 15 patients (14%) had findings indicating PH. The association between pulmonary fibrosis, age, and PH is well known (46) but we also found an association with a low

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**Table 4. Associations between cardiac biomarkers and clinical characteristics in SSc patients, adjusted for age and sex.**

| Characteristics | hs-cTnI β-coefficient | p-value | NT-proBNP β-coefficient | p-value | Uric acid β-coefficient | p-value |
|-----------------|-----------------------|---------|------------------------|---------|------------------------|---------|
| Age             | 0.19                  | 0.05    | 0.45                   | < 0.0001| 0.26                   | 0.007   |
| Gender: female  | -0.25                 | 0.01    | -0.01                  | 0.9     | -0.33                  | 0.0006  |
| Adjusted for age and sex |                   |         |                        |         |                        |         |
| Duration        | -0.17                 | 0.08    | -0.07                  | 0.4     | 0.04                   | 0.7     |
| Subtype lcSSc   | -0.02                 | 0.8     | -0.03                  | 0.7     | -0.10                  | 0.3     |
| Pulmonary fibrosis | 0.13                 | 0.1     | -0.0008                | 1.0     | -0.02                  | 0.8     |
| Suspected PH    | 0.31                  | 0.003   | 0.31                   | 0.001   | 0.12                   | 0.2     |
| PAH             | 0.31                  | 0.001   | 0.27                   | 0.003   | 0.11                   | 0.3     |
| Myositis        | 0.23                  | 0.02    | 0.18                   | 0.05    | -0.04                  | 0.6     |
| Kidney disease  | 0.29                  | 0.002   | 0.42                   | < 0.0001| 0.16                   | 0.07    |
| Skin score      | 0.21                  | 0.03    | 0.29                   | 0.001   | 0.10                   | 0.3     |
| ACA             | -0.04                 | 0.7     | -0.03                  | 0.98    | 0.04                   | 0.7     |
| ATA             | 0.07                  | 0.4     | 0.13                   | 0.15    | 0.17                   | 0.06    |
| ARA             | 0.1                   | 0.25    | 0.23                   | 0.01    | 0.08                   | 0.3     |
| IHD             | 0.29                  | 0.003   | 0.23                   | 0.005   | 0.05                   | 0.5     |
| Ever smoked     | -0.03                 | 0.7     | 0.11                   | 0.23    | -0.02                  | 0.8     |
| BMI (kg/m²)     | 0.06                  | 0.6     | -0.19                  | 0.03    | 0.13                   | 0.1     |
| Systolic BP (mmHg) | -0.05                 | 0.7     | -0.01                  | 0.9     | 0.07                   | 0.5     |
| Diastolic BP (mmHg) | 0.02                  | 0.9     | -0.004                 | 0.9     | 0.07                   | 0.4     |
| Cholesterol (mmol/L) | 0.09                  | 0.4     | -0.22                  | 0.02    | 0.01                   | 0.9     |
| HDL (mmol/L)    | -0.03                 | 0.7     | -0.02                  | 0.8     | -0.09                  | 0.3     |
| LDL (mmol/L)    | 0.08                  | 0.4     | -0.22                  | 0.02    | -0.30                  | < 0.0001|     |
| Triglycerides (mmol/L) | 0.09                  | 0.3     | 0.02                   | 0.8     | 0.35                   | < 0.0001|     |
| Conduction defects | 0.20                  | 0.03    | 0.21                   | 0.02    | 0.1                    | 0.3     |
| P-glucose (mmol/L) | -0.04                 | 0.7     | -0.18                  | 0.05    | 0.13                   | 0.1     |
| CK (mg/L)       | 0.05                  | 0.6     | -0.03                  | 0.8     | -0.08                  | 0.5     |
| eGFR (ml/min/1.73 m²) | 0.31                  | 0.003   | -0.53                  | < 0.0001| -0.26                  | 0.009   |
| hsCRP (mg/L)    | 0.27                  | 0.005   | 0.02                   | 0.9     | 0.25                   | 0.006   |
| ESR (mm)        | 0.29                  | 0.002   | 0.06                   | 0.5     | 0.08                   | 0.4     |

SSc, Systemic sclerosis; hs-cTnI, high-sensitivity cardiac troponin I; NT-proBNP, N-terminal prohormone brain natriuretic peptide; lcSSc, limited cutaneous systemic sclerosis; PH, pulmonary hypertension; PAH, pulmonary arterial hypertension; ACA, anti-centromere antibodies; ATA, anti-topoisomerase 1 antibodies; ARA, anti-RNA polymerase 3 antibodies; IHD, ischaemic heart disease; BMI, body mass index; BP, blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein; CK, creatine kinase; eGFR, estimated glomerular filtration rate; hsCRP, high-sensitivity C-reactive protein; ESR, erythrocyte sedimentation rate. Bold numbers indicate significant p-values (p < 0.05).
eGFR and a trend towards an association with SRC. This finding further highlights the importance of including kidney function when examining cardiac disease in SSc.

We did not adjust for medication in our study, which is a limitation as different drugs can affect both the GFR and the troponin values.

Conclusions

Levels of NT-proBNP and hs-cTnI were higher in SSc patients than controls, and both NT-proBNP and hs-cTnI were associated with pathological findings on echocardiography. Our results thus suggest that hs-cTnI could be a potential biomarker for detecting cardiac involvement in SSc.

SSc patients have a higher prevalence of abnormal echocardiograms than matched population-based controls. As a group, our SSc patients had lower (but normal) LVEF. More SSc patients than controls had regional hypokinesia. We also observed that valvular regurgitation is associated with SSc, while the occurrences of valve thickening and valve prostheses were similar to controls. None of the controls, but 14% of SSc patients, had signs of PH. RV abnormalities were only detected in SSc patients.

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Supplementary Table S1. Characteristics of the 44 patients with echocardiographic abnormalities.

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