Cardiac involvement assessment in systemic sclerosis using speckle tracking echocardiography: a systematic review and meta-analysis

Wei Qiao, Wenjing Bi, Xin Wang, Ying Li, Weidong Ren, Yangjie Xiao

ABSTRACT

Objectives Cardiac involvement in patients with systemic sclerosis (SSc) is associated with poor prognosis. Early detection of myocardial impairment is essential for treatment. The present study aimed to systematically review the value of detecting subclinical myocardial impairment in SSc patients using myocardial strain obtained from speckle tracking echocardiography (STE).

Design A systematic review and meta-analysis.

Data sources The PubMed, Embase and Cochrane library databases were searched in the period from the earliest available indexing date to 30 September 2022.

Eligibility criteria for selecting studies Studies evaluating myocardial function in SSc patients comparison with healthy controls based on myocardial strain data obtained from STE were included.

Data extraction and synthesis Ventricle and atrium data on myocardial strain were extracted to assessing the mean difference (MD).

Results A total of 31 studies were included in the analysis. Left ventricular global longitudinal strain (MD: −2.31, 95% CI −2.85 to −1.77), left ventricular global circumferential strain (MD: −2.93, 95% CI −4.02 to −1.84) and left ventricular global radial strain (MD: −3.80, 95% CI −5.83 to −1.77) was significantly lower in SSc patients than in healthy controls. Right ventricular global wall strain (MD: −2.75, 95% CI −3.25 to −2.25) was also decreased in SSc patients. STE revealed significant differences in several atrial parameters including left atrial reservoir strain (MD: −6.72, 95% CI −10.09 to −3.34) and left atrial conduit strain (MD: −3.26, 95% CI −6.50 to −0.03), as well as right atrial reservoir strain (MD: −7.37, 95% CI −11.20 to −3.53) and right atrial conduit strain (MD: −5.44, 95% CI −9.15 to −1.73). There were no differences in left atrial contractile strain (MD: −1.51, 95% CI −5.34 to 2.33).

Conclusion SSc patients have a lower strain than healthy controls for the majority of STE parameters, indicating the presence of an impaired myocardium involving both the ventricle and atrium.

INTRODUCTION

Systemic sclerosis (SSc), also known as scleroderma, is an immune-mediated rheumatic disease, characterised by fibrosis of the skin and internal organs. SSc is uncommon, but patients with SSc have a high risk of morbidity and mortality. Improved understanding of the condition of patients with SSc could lead to better disease management through accurate staging of the disease and comprehensive assessment of the patient. Cardiac involvement, pathologically manifested as myocardial fibrosis, is a negative prognostic factor when it is clinically evident in SSc patients. Mortality rate is as high as 70% in SSc patients with cardiac involvement, of which 28% is related to cardiac complications. However, cardiac involvement is often asymptomatic, especially in its early stage. Thus, early identification of subclinical cardiac involvement is a major challenge.

Myocardial deformation is considered to be an early indicator of cardiac fibrosis that occurs before myocardial function is significantly impaired. Speckle tracking echocardiography (STE), a recently emerged quantitative ultrasound technique, can be used to estimate myocardial deformation using strain with good feasibility, reproducibility and diagnostic accuracy. Myocardial strain appears to be an optimal quantitative index in several clinical settings, which can especially be used for identification of...
myocardial fibrosis, including hypertrophic cardiomyopathy, and dilated cardiomyopathy.

In the setting of rheumatic disease, STE can provide additional value in the different clinical stages. Changes in myocardial strain reflect myocardial impairment involving both the left and right ventricles in patients with systemic lupus erythematosus. STE is also increasingly used to detect myocardial impairment in patients with SSc based on myocardial strain. However, results from studies are controversial, especially for the entire heart involving both the left and right ventricles in patients with SSc.

The purpose of the present study was to conduct a meta-analysis to characterise cardiac involvement in patients with SSc compared with healthy controls using STE.

METHODS
Screening of publications
A detailed search for studies on STE examination in SSc patients was performed according to Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines. Using the electronic databases of PubMed, Embase and the Cochrane library, publications on STE examination in SSc patients were searched from the earliest available date of indexing up to 30 September 2022. A search strategy was used based on combined the terms: (1) “Speckle tracking” or “Strain” or “STE” and (2) “Echocardiography” or “Echocardiogram” and (3) “Systemic Sclerosis” or “Systemic Scleroderma” (see online supplemental file 1 for detailed search strategy). The present study performed a systematic review and meta-analysis.

Data extraction and quality assessment
Literature extraction was carried out after the search was completed. Studies comparing myocardial strain parameters in SSc patients and healthy controls were included. Duplicate records and studies that did not provide original data and information of interest, such as case reports, conference papers, review articles, letters, basic research studies and non-relevant studies, were excluded. Non-English language articles were also excluded. Two researchers independently reviewed the abstracts of the selected articles using the previous inclusion and exclusion criteria. Disagreements between researchers were resolved via a consensus reached with the help of a third researcher.

Full-text articles containing key parameters were eligible for the final inclusion in the analysis. The key parameters were as follows: values (means with SD or transformed) for left ventricular (LV) global longitudinal strain (LVGLS), LV global circumferential strain (LVGCS) or LV global radial strain (LVGRS) and LV ejection fraction (LVEF), right ventricular global or free wall longitudinal strain (RVFLS), systolic pulmonary artery pressure (sPAP), left atrial (LA) and right atrial (RA) global peak longitudinal strain in systolic period (LA, RAεp: reservoir strain, or LA, RAεpos peak: global/total strain), peak longitudinal strain in early diastole period (LA, RAεCD: conduit strain, or sec LA, RAεneg peak: positive strain) and peak longitudinal strain in late diastole period (LA, RAεCT: contractile strain, or LA, RAεneg peak: negative strain). Data on demographic variables and major clinical variables were also extracted from each study.

Quality of the included studies was assessed using the Newcastle-Ottawa quality assessment scale (NOS) in three broad categories. The scores were displayed on a nine-point scale as poor quality (0–2 points), medium quality (3–5 points) and high quality (6–9 points). Studies of poor quality would be excluded from the analysis.

Risk of bias assessment and sensitivity analyses
Publication bias was assessed by the Egger’s test for included analyses. The random-effect method was used to consider the variability among the included studies. The trim-and-fill method was used to assess the impact of bias. Sensitivity analyses were performed by excluding studies one after another to estimate the stability of the pooled results.

Statistical analysis and meta-regression analysis
Differences in myocardial strain parameters between SSc patients and healthy controls were expressed as mean difference (MD) with pertinent 95% CIs. The pooled effect was tested using Z scores. Heterogeneity among studies was assessed using Cochran’s Q test to measure the inconsistency. The I² statistic was used to describe the proportion of total variation in studies due to heterogeneity. I² statistic <25% indicates low heterogeneity and >50% indicates a high heterogeneity. We hypothesised that inconsistencies among included studies may be affected by demographic variables including number of subjects, gender, mean age and body mass index (BMI), as well as clinical data including duration of disease, diffused type ratio, skin score and Scl-70 positivity rate. To assess the possible effect of these factors on differences across studies, meta-regression analyses were performed using LVGLS, LVGCS, LVGRS, right ventricular global wall strain (RVGLS) or RVFLS as dependent variables (y) and the demographic and clinical covariates as independent variables (x). Statistical analyses were performed using STATA V.15.1 (StataCorp LP). P<0.05 was considered statistically significant.

Patient and public involvement statement
Neither patients nor the public were involved in the design and planning of the study.

RESULTS
Literature search and study selection
A total of 296 records were identified in the electronic databases using the search strategy. The duplicate records (66) were excluded. Additionally, articles that did not provide useful data were excluded, including conference abstracts (119), reviews (19), basic research studies (1), case reports,
editorials, notes and surveys (11), non-relevant records (30), as well as studies not written in English language (2). The remaining 48 studies were further evaluated based on full-text articles, of which 17 articles were excluded due to insufficient data. Finally, the remaining 31 studies were included in the meta-analysis to calculate pooled MDs. Of these, 22 were used for LV analysis, 16 for RV analysis, 7 for LA analysis and 3 for RA analysis. The study selection procedure is shown in figure 1.

Figure 1 Publication screening flow chart. LA, left atrial; RA, right atrial; LV, left ventricle; RV, right ventricle.

Study characteristics
In total, 31 studies with 1985 SSc patients and 1212 healthy controls were included. These studies were published between 2011 and 2022. All included studies had a case-control design, and in the majority of studies, the controls were matched based on age and sex. The average age of the patient group and control group was 51.1 and 50.2 years, respectively. The characteristics of the studies and the participants are summarised in table 1.

Publication bias and sensitivity analyses
Publication bias was non-significant for LVGLS (P for Egger’s test=0.119), LVGCS (P for Egger’s test=0.819) and LVEF (P for Egger’s test=0.744). There was also no publication bias for RVGLS (P for Egger’s test=0.286), RVFLS (P for Egger’s test=0.835) and sPAP (P for Egger’s test=0.430). Furthermore, publication bias was not significant for LAεCD (P for Egger’s test=0.827), LAεCT (P for Egger’s test=0.695) and RAεR (P for Egger’s test=0.732). There was publication bias for LVGRS (P for Egger’s test=0.021) and LAεR (P for Egger’s test=0.042). The trim-and-fill method was then used to obtain the corrected pooled values for LVGRS and LAεR. Publication bias test was not applicable for RAεCD because too few studies were included. Sensitivity analysis was performed to explore the stability of the results. None of the studies had a significant effect on pooled strain, which supports the robustness of the results.

Quality assessment
All of the included studies were of high quality based on NOS, with 17 studies receiving 7 points and 14 studies receiving 6 points. No study was excluded for analysis. The scores for each study are presented in table 1.

Comparison of myocardial strain between SSC patients and healthy controls based on LV strain assessed by STE
In total, 22 studies were included in the analysis of LV strain. Of these, all studies reported data on LVGLS in 1368 SSc patients and 865 healthy controls, 10 studies reported data on LVGCS in 395 SSc patients and 405 healthy controls and 7 studies reported data on LVGRS in 376 SSc patients and 229 healthy controls. In addition, there were 22 studies reporting LVEF in 1368 SSc patients and 865 healthy controls. LVGLS (MD: −2.31, 95%CI −2.85 to −1.76, p=0.000; I²=85.1%; figure 2A), LVGCS (MD: −2.93, 95%CI −4.02 to −1.84, p=0.000; I²=74.4%; figure 2B) and LVGRS (MD: −3.80, 95%CI −5.83 to −1.77, p=0.000; I²=28.8%; figure 2C) were significantly lower in SSc patients than in healthy controls. LVGRS was also significantly lower in SSc patients than in healthy controls (MD: −2.17, 95%CI −2.56 to −0.84, p=0.000; I²=83.7%) but within the normal range (see online supplemental file 1).

RV strain assessed by STE
In total, 16 studies were included in the analysis of RV strain. Of these, 13 studies reported data on RVGLS in 729 SSc patients and 494 healthy controls, and five data on RVFLS in 308 SSc patients and 187 healthy controls. In addition, 12 studies reported on sPAP in 802 SSc patients and 471 healthy controls. RVGLS (MD: −2.75, 95%CI −3.25 to −2.25, p=0.000; I²=17.1%; figure 3A) and RVFLS (MD: −3.67, 95%CI −5.49 to −1.86, p=0.000; I²=76.3%; figure 3B) were significantly lower in SSc patients than in healthy controls. In addition, sPAP was significantly higher in SSc patients than in healthy controls (MD: 9.19, 95%CI 6.82 to 11.57, p=0.000; I²=88.8%), which cannot be defined as pulmonary hypertension (see online supplemental figure S2).

LA strain assessed by STE
In total, seven studies were included in the analysis of LA strain. Of these, all studies reported data on LαεR in 356 SSc patients and 242 healthy controls, four studies reported data on LαεCD in 211 SSc patients and 131 healthy controls and three studies reported data on LαεCT in 158 SSc patients and 105 healthy controls. LαεR (MD: −6.72, 95%CI −10.09 to −3.34, p=0.000; I²=89.4%; figure 4A) and LαεCD (MD: −3.26, 95%CI −6.50 to −0.03, p=0.048; I²=89.8%; figure 4B) was significantly lower in SSc patients than in healthy controls, while LαεCT was not (MD: −1.51, 95%CI −5.34 to 2.33, p=0.441; figure 4C).
## Table 1  Study characteristics

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<td>54±7</td>
<td>NR</td>
<td>7.2±5.8</td>
<td>54.3</td>
<td>NR</td>
<td>NR</td>
<td>EPiq 7, Philips; Qlab</td>
<td>RA</td>
<td>RAaR, RAaCD, RAaCT</td>
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<tr>
<td>Guerra et al²⁶</td>
<td>Italy</td>
<td>2018</td>
<td>104</td>
<td>88.5</td>
<td>54.6±16.1</td>
<td>53.9±16.6</td>
<td>23.3±4.7</td>
<td>NR</td>
<td>34.6</td>
<td>NR</td>
<td>51.9</td>
<td>Vivid 7 Pro, GE; EchoPAC</td>
<td>LV, RV</td>
<td>LVGLS, RVGLS</td>
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<tr>
<td>Zairi et al²⁴</td>
<td>Tunisia</td>
<td>2019</td>
<td>50</td>
<td>98.0</td>
<td>53.6±3.456</td>
<td>60.8±8.72</td>
<td>25.1±5.6</td>
<td>NR</td>
<td>92.0</td>
<td>NR</td>
<td>NR</td>
<td>Vivid 9, GE; EchoPAC</td>
<td>LV, RV</td>
<td>LVGLS, RVGLS</td>
<td>7</td>
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<tr>
<td>Şahin et al²⁶</td>
<td>Turkey</td>
<td>2019</td>
<td>67</td>
<td>NR</td>
<td>48.2±12.4</td>
<td>47.5±9.4</td>
<td>NR</td>
<td>8.8±8.2</td>
<td>25.5</td>
<td>11.1±5.5</td>
<td>0.4</td>
<td>C256, Siemens; IE33, Philips; Qlab</td>
<td>LV, RV</td>
<td>LVGLS, RVGLS</td>
<td>6</td>
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<tr>
<td>Tountas et al²⁵</td>
<td>Greece</td>
<td>2019</td>
<td>149</td>
<td>86.6</td>
<td>53.3±13.7</td>
<td>53.5±12</td>
<td>NR</td>
<td>7±2</td>
<td>41.0</td>
<td>NR</td>
<td>70.5</td>
<td>Vivid 7 pro, GE; EchoPAC</td>
<td>LV, RV</td>
<td>LVGLS, LVGCS, RVFLS</td>
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<tr>
<td>Tenneø et al²⁶</td>
<td>Norway</td>
<td>2019</td>
<td>257</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>24±4</td>
<td>1.7±5.4</td>
<td>6±7.4</td>
<td>NR</td>
<td>NR</td>
<td>Vivid 7 or Vivid E8, GE; EchoPAC</td>
<td>LV</td>
<td>LVGLS, LVGCS</td>
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<tr>
<td>Karadag et al²⁷</td>
<td>Turkey</td>
<td>2020</td>
<td>83</td>
<td>92.6</td>
<td>52.1±12.4</td>
<td>49.4±8.4</td>
<td>27.4±4.8</td>
<td>8.5±5.9</td>
<td>70.2</td>
<td>NR</td>
<td>NR</td>
<td>Vivid 7, GE; EchoPAC</td>
<td>LV, RV</td>
<td>LVGLS, RVGLS</td>
<td>7</td>
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<tr>
<td>Hajsadeghi et al²⁴</td>
<td>Iran</td>
<td>2020</td>
<td>60</td>
<td>71.7</td>
<td>45.9±11.73</td>
<td>43.76±12.93</td>
<td>23.1±3.7</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>IE33, Philips; Qlab</td>
<td>LV</td>
<td>LVGLS</td>
<td>6</td>
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<tr>
<td>Mercurio et al²⁵</td>
<td>USA</td>
<td>2021</td>
<td>218</td>
<td>86.7</td>
<td>54.3±12.6</td>
<td>53.9±15.4</td>
<td>26.0±5.8</td>
<td>16.0±11.2</td>
<td>39.9</td>
<td>NR</td>
<td>NR</td>
<td>IE33, Philips; Qlab</td>
<td>LV</td>
<td>LVGLS</td>
<td>7</td>
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<tr>
<td>Demirci et al²⁶</td>
<td>Turkey</td>
<td>2021</td>
<td>100</td>
<td>89.0</td>
<td>50.5±11.3</td>
<td>46.5±10.2</td>
<td>27.3±4.4</td>
<td>5.2±5.1</td>
<td>38.2</td>
<td>NR</td>
<td>NR</td>
<td>EPiq 7, Philips; Qlab</td>
<td>LV, RV</td>
<td>LVGLS, RVGLS</td>
<td>6</td>
</tr>
<tr>
<td>Sharifkazemi et al²⁰</td>
<td>Iran</td>
<td>2022</td>
<td>74</td>
<td>67.6</td>
<td>46.97±1.15</td>
<td>44.43±11.93</td>
<td>24.7±3.6</td>
<td>9.62±6.02</td>
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<td>NR</td>
<td>NR</td>
<td>SC2000, Siemens; NR</td>
<td>LV, RV, LA, RA</td>
<td>LVGLS, LVGCS, LAaR, RAaR</td>
<td>7</td>
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BMI, body mass index; FLS, free wall longitudinal strain; GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; LA, left atrium; LV, left ventricle; NOS, Newcastle-Ottawa quality assessment scale; NR, no report; RA, right atrium; RV, right ventricle; εCD, conduit strain; εCT, contractile strain; εR, reservoir strain.
RA strain assessed by STE
In total, three studies were included in the analysis of RA strain. Of these, all of the studies reported data on RAεR in 147 SSc patients and 102 healthy controls, and two studies reported data on RAεCD in 110 SSc patients and 65 healthy controls. RAεR was significantly lower in SSc patients than healthy controls (MD: −7.37, 95% CI −11.20 to −3.53, p=0.000; I² =25.6%; figure 5A). RAεCD was also significantly lower in SSc patients than in healthy controls (MD: −5.44, 95% CI −9.15 to −1.73, p=0.004; I² =66.0%; figure 5B).

Meta-regression analysis
Meta-regression models showed no significant association between the myocardial strain parameters, including LVGLS, LVRCS, LVGRS, RVGLS and RVFLS, and demographic variables including number of subjects, mean age, gender and BMI, as well as clinical data including duration of disease, diffused type ratio, skin score and Scl-70 positivity rate (see online supplemental file 1).

DISCUSSION
Detection and monitoring of myocardial impairment using appropriate and accurate diagnostic tools is an important aspect of managing patients with SSc. Efforts have been made in early targeted therapy for cardiac involvement in SSc patients. Advanced imaging modalities such as cardiac MRI should only be used for...
further evaluation of individuals with suspected cardiac involvement. Cardiac MRI can detect cardiac involvement in the early stages of SSC. However, the costs and availability of cardiac MRI make it challenging for use as an initial screening test. STE is a sensitive tool to assess cardiac involvement, which may also identify early signs of cardiac involvement in patients with SSC. This is the first meta-analysis assessing cardiac involvement, including the ventricles and atria, in SSC patients using STE.

GLS, GCS and GRS are used as speckle tracking indexes to evaluate ventricles. They represent myocardial deformation in different motion directions. The present study showed that SSC patients exhibited reduced LVGLS, LVGCS and LVGRS compared with healthy controls, although some studies have had different conclusions. Cadeddu et al. have reported reduced LVGLS compared with controls only during exercise. Durmus et al. have found that LVGLS, LVGCS and LVGRS were similar between the two groups. Spethmann et al. have reported that only LVGLS was decreased but not LVGCS and LVGRS. Yiu et al. have shown decreased levels of LVGLS and LVGCS but not of LVGRS. Zairi et al. have demonstrated altered levels of LVGLS with variation between individuals. The results of a single study with a relatively small sample size could be affected by many factors, including duration of disease and disease type ratio, which may lead to different strain changes. In addition, the pooled LVEF was decreased in SSC patients compared with the control group, despite being within the normal range, suggesting that its tendency to decrease likely occurred at time points following strain changes. Overall, the pooled data did not only confirm the usefulness of STE, but also indicated that cardiac involvement occurs in SSC patients. The decreased myocardial strain showed myocardial impairment in the LV.

Longitudinal strain was also used for RV analysis. Several studies have found no difference in results: Karadag et al. have shown preserved RV strain, and Pigatto et al. have demonstrated no difference between the two groups. The present meta-analysis confirmed the decreased pooled RV strain. Although no overt pulmonary hypertension
(sPAP >35 mm Hg) was noticed in SSc patients, sPAP was significantly elevated in patients compared with healthy controls. Thus, the pressure overload caused by pulmonary fibrosis complicated the assessment of intrinsic myocardial involvement.

Speckle tracking index for evaluation of atrium mechanics includes εR, εCD and εCT. Tigen et al.\(^\text{[27]}\) have reported that LA reservoir and conduit functions were similar between the groups, but other studies have reported one or more decreased LA mechanics indexes.\(^\text{[28–31]}\) The present meta-analysis showed that εR and εCD were decreased, whereas no significant differences were found for εCT. For RA, εR was also confirmed to be decreased. Although only two studies\(^\text{[21, 32]}\) were included in the evaluation of εCT, they both showed impaired RA mechanics with decreased εCD. There are relatively few related studies performing a trial analysis, and further research is needed to support this conclusion.

Furthermore, although all included studies were of high quality, a significant heterogeneity was observed among most groups of studies reporting on different indexes. We found no demographic variables or clinical factors that were associated with STE parameters and could account for the heterogeneity. Some potential limitations of our study need to be discussed. First, the included studies were observational, which makes selection and observer bias unavoidable. Moreover, publication bias was also present for some indexes, although it did not change the result. Second, methods used to identify relevant studies were limited to publications in English language, potentially missing relevant published data. Third, the meta-regression analysis did not identify factors associated with heterogeneity, since there were characteristics and information data missing in each study. Lastly, significant heterogeneity can be partly explained by the differences in equipment and software used to detect myocardial strain.

**CONCLUSION**

Our meta-analysis showed that SSc patients have a lower strain than healthy controls for the majority of STE parameters in both the ventricle and atrium. These findings demonstrate the presence of subclinical cardiovascular abnormalities in SSc patients that can be detected by STE.

**Competing interests** We have read and understood the BMJ policy on declaration of interests and declare that we have no competing interests.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Ethics statement** This study was a systematic review and meta-analysis. Ethics committee approval was not necessary, because all data were carefully extracted from existing literatures.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** All data relevant to the study are included in the article or uploaded as supplementary information.

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