

# Evaluation of Cardiac Function in Systemic Sclerosis with Novel Echocardiographic Technologies

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## Abstract

Systemic sclerosis (SSc) is a connective tissue disease characterized by widespread vascular lesions. Primary myocardial involvement is common in SSc and, when clinically evident, appears as a poor prognostic factor. Using conventional methods, myocardial perfusion impairment and biventricular dysfunction have been reported in SSc. Recently, Tissue Doppler Imaging (TDI) echocardiography and magnetic resonance imaging have confirmed these results. TDI, with its derived strain, strain rate and myocardial performance index, is a powerful new echocardiographic tool that is now becoming the standard for assessing ventricular function in a variety of situations and diseases. In the present article we review the main published data on the application of TDI in the evaluation of cardiac function and prediction of prognosis in patients with SSc.

## INTRODUCTION

Systemic sclerosis (SSc) is a multisystem disorder characterized by diffuse vascular lesions and fibrosis of the skin and internal organs (1,2). Cardiac involvement is a common finding in SSc, but often clinically occult. In fact, clinical evidence of myocardial disease may be found in 20-25% of patients with SSc, while at postmortem examination the heart is affected in up to 80% of patients (3,4). The course and prognosis are highly dependent on the clinical pattern, and the main causes of death are cardiovascular, renal and pulmonary disease. Heart involvement is one of the main factors shortening the survival of SSc patients (5). Although cardiac abnormalities could be more prevalent and severe in the diffuse cutaneous subtype of the disease, there is increasing evidence suggesting that cardiac involvement is also a frequent finding in the limited cutaneous subtype. In the large epidemiological Italian study, although heart symptoms were found more frequently in the diffuse form (32%) as compared with the limited form (23%), the difference was not statistically significant (6). Some data have even suggested a more prevalent involvement in the limited subtype of the disease (7).

Magnetic resonance imaging, single photon emission computed tomography, echocardiography and radionuclide ventriculography have been used to investigate myocardial perfusion and contractility. The data showed that myocardial

perfusion abnormalities together with various degrees of biventricular dysfunction were common. Moreover, echocardiography and radionuclide ventriculography may be influenced by loading conditions and adjacent segment motion (8,9). Tissue Doppler Imaging (TDI) has been introduced as a quantitative, more objective, and sensitive method for the assessment of myocardial function. It is a new approach that allows direct and valid measurement of myocardial velocities and strain rate (10,11). Myocardial strain rate has been shown to be a strong index of contractility, independent of myocardial translation and less dependent on loading conditions. Furthermore, strain rate determined by TDI is a more sensitive method than conventional echocardiography or radionuclide ventriculography for detecting changes in myocardium contractility (12,13,14). The myocardial performance index has been considered a good predictor for adverse results in several cardiac diseases, such as valvular insufficiency, cardiomyopathies and acute myocardial infarction. It is easy to obtain, however, using TDI to obtain myocardial performance index (representing regional systolic and diastolic function) is not a universally accepted method (15,16,17).

Based on these grounds, the purpose of the present review is to describe the rationale behind and clinical use of TDI, strain rate and myocardial performance index in the assessment cardiac function, prediction of prognosis and distinguishing cutaneous subtypes in patients with SSc, and

their relation to other instrumental features of the disease, with focus on recent developments (Table 1).

**Figure 1**

Table 1: Baseline characteristics

Study	No. of patients	Male/ Female	Age (years)	Disease duration (years)	Pulmonary systolic pressure(mmHg)	Ejection fraction*% by echocardiogram
Can et al 2007 (18)	24	4/20	49 ± 11	NA	NA	LV: 69 ± 5.1
Allanore et al 2006 (19)	18	4/18	54.2 ± 10.4	6.6 ± 5.9	32 ± 5	NA
Hsiao et al 2006 (20)	40	15/25	46 ± 16	Diffuse: 6.7 ± 3.3 Limited: 10.8 ± 3.3	35.2 ± 13*	LV: 61.7 ± 5.8 Right ventricle: 39.2 ± 6.7*
D'Andrea et al 2005 (21)	23	3/20	56.3 ± 8.2	NA	43.2 ± 9.8*	LV: 55.7 ± 6.7
Gullulu et al 2005 (22)	22	2/20	50.2 ± 4.8*	8.7 ± 8.5	23.7 ± 20.5	LV: 64 ± 8.4*
Lindqvist et al 2005 (23)	26	5/21	56 ± 15	11.8 ± 8.7	22.1 ± 5.8	LV: 57.2 ± 10.3
Misme et al 2005(24)	17	3/14	54.3 ± 8.1	7.2 ± 3.5	33.1 ± 6	LV: 66.9 ± 8.4
Vignaux et al 2005 (25)	18	4/14	59 ± 8.9	7.2 ± 4.3	32 ± 4	NA
Flizak et al 2002 (4)	19	0/19	Mean = 51.7	Mean = 13.4	28.4 ± 10.9*	LV: 67.4 ± 11.4

\*Statistically significant (p<0.05) in patients with SSc relative to control subjects  
LV: left ventricle

These techniques provide accurate information about segmental myocardial motion and deformation during the cardiac cycle and offer the advantage, with respect to conventional Doppler echocardiography, of assessing systolic and diastolic function of both the ventricles at a regional level (12,13,14).

**A HIGHLIGHT ON THE USE OF TDI IN THE ASSESSMENT OF MYOCARDIAL FUNCTION**  
**RIGHT VENTRICULAR FUNCTION**

The early detection of right ventricular dysfunction may be important in clinical practice. However, this issue has not been sufficiently investigated by non-invasive techniques because of right ventricular complex geometry which hinders an accurate assessment of right ventricular internal chamber dimensions and their changes during the cardiac cycle (23). Lindqvist et al focused on right ventricular diastolic function in 26 consecutive SSc patients compared with 25 matched controls; TDI showed that both global and regional isovolumic relaxation times were prolonged (p<0.001) in SSc patients with no significant changes regarding right ventricular systolic function (23). Another study revealed that the tricuspid annular isovolumic relaxation time (p=0.001) and the tricuspid E/E' ratio (p=0.04) were significantly increased in 22 SSc patients compared with the 22 healthy volunteers (22). D'Andrea et al showed that TDI analysis detected impaired myocardial right ventricular early-diastolic peak velocities (P<0.0001) and

prolonged myocardial time intervals at tricuspid annulus in 23 SSc patients (21). Finally, in a recent study of 40 consecutive SSc patients compared with 45 matched controls, the subclinical right ventricular dysfunction was more common than predicted. Fifty-five % of the patients had right ventricular systolic dysfunction (right ventricular ejection fraction <40%), and TDI uncovered that peak myocardial systolic velocity (p<0.001) as well as early and late diastolic velocities were prolonged (p=0.01 and 0.05 respectively) (20).

**LEFT VENTRICULAR FUNCTION**

Previous studies using conventional measurements have reported low prevalence of systolic dysfunction and variable alteration in diastolic function in SSc. However, left ventricular (LV) dysfunction might be underestimated by conventional measurements (8, 24). A study of 19 SSc women pointed out that early diastolic velocities were significantly lower (p<0.00001) in comparison to 16 control healthy women. Also, the detailed assessment of diastolic function in the SSc group showed severe diastolic dysfunction of longitudinal myocardial fibers with normal function of circumflex myocardial fibers (4). Another study found that mitral annular isovolumic relaxation time was significantly increased (p=0.03) in SSc patients (22). D'Andrea et al showed that the myocardial early diastolic wave /myocardial atrial diastolic wave ratio was significantly lower (p<0.01) in SSc patients compared with the control group while Hsiao et al showed similar TDI parameters between the 2 groups (20,21).

**ATRIAL CONDUCTION**

Can et al studied 24 SSc patients and 24 control subjects. There was a delay between the onset of the P wave on surface electrocardiogram and the onset of the late diastolic wave in SSc patients measured at lateral septal annulus (p=0.001), septal mitral annulus (p = 0.01) and tricuspid annulus (p = 0.05). Interatrial conduction time was also delayed. They concluded that atrial conduction abnormalities are significantly higher in SScs patients with delay in both intraatrial and interatrial electromechanical coupling intervals (18).

Therefore, it appears that in progressive SSc, myocardial dysfunction is common and detailed screening of cardiac function in SSc patients with TDI is warranted for early detection of abnormalities.

### **STRAIN AND STRAIN RATE DERIVED TDI IN THE DETECTION OF MYOCARDIAL ABNORMALITIES**

Strain rate imaging has been recently developed to measure regional velocity gradients. This technique overcomes several limitations inherent in measuring regional velocity profiles, because it is not influenced by global cardiac displacement and the tethering effects of adjacent segments (26). Meune et al detected that SSc patients had lower systolic strain rate ( $p < 0.0001$ ) and lower diastolic strain rate ( $p = 0.0004$ ) than controls; 10/17 SSc patients had reduced systolic strain rate and 11/17 patients had reduced diastolic strain rate despite normal LV ejection fraction (24). D'Andrea et al perceived that peak systolic strain rate and strain were both reduced in the basal, middle and apical right ventricular lateral free walls, and in the basal and middle LV lateral walls in SSc patients (21). Vignaux et al prospectively evaluated 18 patients with SSc without clinical heart failure and with normal pulmonary arterial systolic pressure. TDI was assessed at baseline, after a 72 hour vasodilator washout period, and after 14 days of oral treatment with nifedipine. Nifedipine treatment led to a significant increase in the magnetic resonance imaging perfusion index ( $p = 0.0003$ ) and in systolic and diastolic strain rate ( $p = 0.0002$  and  $p = 0.0003$ , respectively) (25). Similar findings were discovered in 18 SSc patients with lower systolic and diastolic strain rate in comparison with 15 healthy subjects. Median peak systolic strain rate was markedly improved ( $p = 0.0002$ ) after bosentan treatment. Bosentan also significantly increased the median peak early diastolic strain rate function ( $p = 0.0003$ ) (19). To sum up, Strain and strain rate are respective markers of regional contractility and diastolic function.

### **MYOCARDIAL PERFORMANCE INDEX AS A SURROGATE OF MYOCARDIAL PERFORMANCE**

The myocardial performance index assesses the global functions of the ventricles and is not influenced by factors such as pre and after-load (22). Hsiao et al found the myocardial performance index of right ventricle did represent ventricular function. The myocardial performance index of the right ventricle in patients with SSc was much higher than in control subjects ( $p < 0.0001$ ). Furthermore, the difference in myocardial performance index between control and SSc groups was more prominent in the right ventricle and septum than in the LV lateral wall (20).

### **TDI AS A PREDICTOR OF PROGNOSIS AND**

### **OUTCOME**

As most of the work in TDI has been diagnostic in nature, there has been a great interest in the prognostic implications of TDI diastolic variables. Lindqvist et al noticed a significant correlation between forced vital capacity/ Carbon monoxide diffusing capacity and isovolumic relaxation time/R-R time interval ( $r = 0.44$ ,  $p < 0.05$ ). These findings appear to be early markers of right ventricular disturbance, probably in response to intermittent pulmonary arterial hypertension (23). D'Andrea et al pointed out an independent inverse association of right ventricular peak early-diastolic velocity with both Rodnan Skin Score (1,27) ( $p < 0.0005$ ) and pulmonary arterial systolic pressure ( $p < 0.0001$ ), as well as independent inverse correlation of the same right ventricular peak early-diastolic velocity with pulmonary fibrosis ( $p < 0.0005$ ). In addition, right ventricular peak early-diastolic velocity was an independent predictor of the anti Scl-70 antibody pattern ( $p < 0.001$ ). Those findings indicate how the right ventricular dysfunction in SSc occurs concomitantly with the pulmonary hypertension and skin involvement. They may also be valuable to distinguish patients with a more aggressive and diffuse form of the disease (21). Hsiao et al uncovered that right ventricular - myocardial systolic velocity  $< 11$  cm/s indicated right ventricular ejection fraction  $< 40\%$  with sensitivity of 87% and specificity of 86%. In addition, right ventricular - myocardial systolic velocity  $< 12$  cm/s was associated with more frequent hospital admission. They assumed that the myocardium surrounding the right ventricle can be used to predict the hospital readmission rate of patients with SSc (20). Finally, Allanore et al and Vignaux et al demonstrated the strikingly beneficial short term myocardial effects of both nifedipine and bosentan in patients with SSc determined by magnetic resonance imaging and TDI (19, 25).

### **APPLICATION OF TDI IN DISTINGUISHING THE CUTANEOUS SUBTYPES**

Although cardiac abnormalities could be more prevalent and severe in the diffuse SSc, there is increasing evidence suggesting that cardiac involvement is also a frequent finding in the limited subtype (28). Plazak et al and Vignaux et al showed no significant difference between the diffuse (42% and 56% respectively) and limited (58% and 44% respectively) subtypes (4, 25). In the study by Meune et al, patients with diffuse SSc (47%) had reduced mean forced vital capacity ( $p = 0.006$ ) and mean Carbon monoxide diffusing capacity / hemoglobin ( $p = 0.03$ ) when compared with limited subtype (53%), but there was no difference

regarding thallium perfusion score, LV ejection fraction, echocardiographic parameters and TDI values (24). Another study encountered that patients with the limited subtype (60%) were older with longer disease duration. Patients with diffuse SSc (40%) had lower forced vital capacity and Carbon monoxide diffusing capacity with higher pulmonary arterial systolic pressure. The TDI parameters were similar except for the myocardial performance index of the right ventricle (lower in diffuse SSc,  $p = 0.03$ ) in both forms. Patients with diffuse SSc had a trend toward more frequent hospitalization (20). To conclude, these studies may represent the severity of heart involvement which was nearly equal regardless of subtype presumably due to the high prevalence of myocardial dysfunction in both SSc subtypes.

### CONCLUSIONS

The present review proposes that pulsed TDI, which is far more sensitive than conventional techniques, is a valuable non-invasive and easy-repeatable tool for detecting early myocardial involvement, predicting the prognosis and for follow-up in patients with SSc. There is a high prevalence of abnormal myocardial systolic and diastolic function in SSc patients, despite normal global ejection fraction of both ventricles. Another important clinical implication is that biventricular function should be studied in detail in patients with SSc. Detection of abnormalities in diastolic function might provide a means of identifying patients at risk for progressive heart failure. There was a high prevalence of myocardial dysfunction of both SSc forms. Finally, there was a strikingly beneficial short term myocardial effect of vasodilators in patients with SSc.

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