# Left Ventricular Diastolic Function in Systemic Sclerosis: Assessment by Radionuclide Angiography

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The aim of this study was to assess left ventricular function in subjects with systemic sclerosis. Twenty-four women with systemic sclerosis (mean age 48 ± 11 yr) and 14 age- and sex-matched normal subjects were studied by radionuclide angiography performed at rest with a temporal resolution of 20 msec/frame. Left ventricular volume curves were generated and indices of systolic and diastolic function were computed. Left ventricular diastolic asynchrony was evaluated by dividing the left ventricle into five regions and then computing the time-to-peak filling rate for each region. After excluding the valvular region, the coefficient of variation of this index was obtained. The isovolumic relaxation period was prolonged in systemic sclerosis patients in comparison to normal subjects (127 ± 39 msec versus 87 ± 44 msec, $p < 0.05$). Moreover, 38% of the systemic sclerosis patients had a subnormal peak filling rate. Left ventricular diastolic asynchrony was increased in the systemic sclerosis group, as expressed by a higher coefficient of variation of the regional time to peak filling rate (27.9% ± 11.5% versus 14.5% ± 8.6%, $p < 0.05$). Our results indicate an impaired relaxation and an increased diastolic asynchrony in patients with systemic sclerosis.

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Cardiac involvement is a relatively common occurrence in systemic sclerosis (*1*). When this complication is clinically recognizable, the prognosis is usually poor. Moreover, radionuclide studies indicate that perfusion and systolic function abnormalities are often present without clinical evidence of cardiac involvement (*1,2*). Recently, impaired left ventricular (LV) diastolic function has been demonstrated by doppler echocardiography (*3*).

The aim of this study was to evaluate LV diastolic function by radionuclide angiography in patients with systemic sclerosis without evident cardiac involvement.

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## MATERIALS AND METHODS

Twenty-four patients with systemic sclerosis were selected for this study. Patients with known pulmonary hypertension, myocardial or renal involvement were excluded. All patients were female, with a mean age of 48 ± 11 yr. All patients satisfied the major preliminary criterion for classification of a disorder as definite systemic sclerosis, which requires only scleroderma of the extremities proximal to the digits (*4*). In 16 patients, the scleroderma was limited to the skin of the hands, the arms, and/or the thighs, while in 8 patients the scleroderma also involved the thorax and/or the abdomen. Ten patients had the Crest syndrome variant (calcinosis, Raynaud's esophageal dysmotility, sclerodactily, and teleangiectasia). The control subjects were 14 normal healthy women (mean age 50 ± 11 yr).

Radionuclide angiography was performed with the patient at rest in the supine position. Red blood cells were labeled in vivo with 20–25 mCi of $^{99m}$Tc and counts were collected by a small field of view Anger camera (Siemens LEM ZLC) oriented to a 45-degree left anterior oblique view with a 15-degree caudal tilt. Images were acquired with a 2× digital zoom, in frame mode, at a framing rate of 20 msec/frame with a gate tolerance of ±5%, collecting at least 150,000 counts/frame. Left ventricular and background regions of interest were automatically drawn on both end-diastolic and end-systolic frames and from these areas four time-activity curves were obtained. The final curve was obtained by weighted interpolation of end-diastolic and end-systolic curves after subtraction of the corresponding background curve. Ejection fraction was calculated on the "raw" time-activity curve, whereas the other indices were computed after filtering using a Fourier expansion with four harmonics. Peak filling rate (PFR) was computed as the maximum on the first derivative of the time-activity curve and normalized by the end-diastolic number of counts. Time-to-peak filling rate (TPFR) was defined as the interval from end-systole to PFR. The first third filling fraction was computed as the counts at one-third of diastole minus the counts at end-systole and expressed as percentage of stroke counts (*5*). The isovolumic relaxation period (IRP) was measured according to the method proposed by Betocchi et al. (*6*). Briefly, IRP was considered as the interval between end-systole and the onset of rapid filling, automatically identified on the second derivative of the time-activity curve. It was possible to measure IRP in 14 patients and in 12 normal subjects. Further details on the radionuclide angiography methods and on the accuracy and reproducibility of these measurements in our laboratory have been previously reported (*7*).

Right ventricular ejection fraction was determined by manual edge determination utilizing the method of Maddahi et al. (*8*).

Left ventricular regional analysis was performed using a computer algorithm that identified the center of gravity of the LV region of interest and divided it into five sectors of equal angles starting at 3 o'clock and proceeding counterclockwise (*9*). The sector that includes the mitral and aortic valves was not used in the analysis. Time-activity curves were filtered, after background subtraction, using a Fourier expansion with three harmonics. All indices computed from the global time-activity curve were also calculated for each region. We evaluated LV systolic and diastolic asynchrony by measuring the coefficient of variation (CV) of the four regional values of time to end-systole (CV-TES) and time-to-peak filling rate (CV-TPFR), respectively.

The lung-to-heart ratio was also computed as an index of pulmonary blood volume. A region of interest was drawn over the left lung taking care not to include the aorta and sampling a minimum of 1,360 counts (*10*). An equal size region of interest was then placed over the left ventricle. The lung-to-heart ratio was computed as the average counts per pixel of the lung region divided by the average counts per pixel of the left ventricular region.

Routine spirometry was also performed in all patients: restrictive lung disease was graded as absent (forced vital capacity above 80% of the predicted normal), mild (forced vital capacity 66%–80% of predicted), moderate (forced vital capacity 50%–65% of predicted), or severe (forced vital capacity below 50% of predicted).

Data are expressed as mean ± standard deviation. Student's t-test and regression analysis were used as appropriate. The Bonferroni correction was used for multiple group comparison.

## RESULTS

Table 1 shows the results obtained in the systemic sclerosis group and in normal subjects. Although both PFR and TPFR were similar in the two groups, 9 of the 24 patients (38%) had PFR less than 2.8 end-diastolic volumes per sec [the lower limit of normal in our laboratory (*7*)]. The IRP was prolonged in patients with systemic sclerosis. The CV-TPFR was significantly higher in the systemic sclerosis group. The first third filling fraction was significantly lower in the patients with systemic sclerosis than in normal subjects. The lung-to-heart ratio was higher in the systemic sclerosis group, but this difference was not significant. Moreover, a positive correlation between PFR and the lung-to-heart ratio was found in the patient group ($r = 0.60$, $n = 24$, $p < 0.05$). Figure 1 shows an example of abnormal diastolic function in a patient with systemic sclerosis.

Left ventricular ejection fraction (LVEF) was slightly higher (although the difference did not reach the significant level) in the 10 patients with Crest syndrome than that found in the 14 patients with diffuse scleroderma, 2 of whom (14%) had an abnormal LVEF at rest. Moreover, the mean value of LVEF in the group of patients with diffuse scleroderma was significantly lower than that found in the control group (Table 2). The IRP was prolonged in both groups, although the difference from the control

**TABLE 1**
Cardiac Function in Patients with Systemic Sclerosis and in Normal Subjects

| Variable | Normals | Systemic sclerosis patients | p Value |
|---|---|---|---|
| Age | 50 ± 11 | 48 ± 11 | ns |
| Heart rate (bpm) | 73 ± 11 | 74 ± 12 | ns |
| LVEF | 70 ± 7 | 66 ± 8 | ns |
| PFR | 3.3 ± 0.5 | 3.4 ± 1.1 | ns |
| TPFR | 171 ± 58 | 175 ± 39 | ns |
| IRP | 87 ± 44 | 127 ± 39 | <0.05 |
| CV-TES | 14.9 ± 7.1 | 15.4 ± 7 | ns |
| CV-TPFR | 14.5 ± 8.6 | 27.9 ± 11.5 | <0.05 |
| 1/3 FF | 31 ± 13 | 24 ± 8 | <0.05 |
| RVEF | 47 ± 7 | 47 ± 6 | ns |
| L/H | 0.46 ± 0.06 | 0.51 ± 0.11 | ns |

LVEF = left ventricular ejection fraction (%); PFR = peak filling rate (end-diastolic volumes per sec); TPFR = time-to-peak filling rate (msec); IRP = isovolumic relaxation period (msec); CV-TES = coefficient of variation of regional time to end-systole (%); CV-TPFR = coefficient of variation of regional time-to-peak filling rate (%); 1/3 FF = first third filling fraction (%); RVEF = right ventricular ejection fraction (%); and L/H = lung-to-heart ratio.

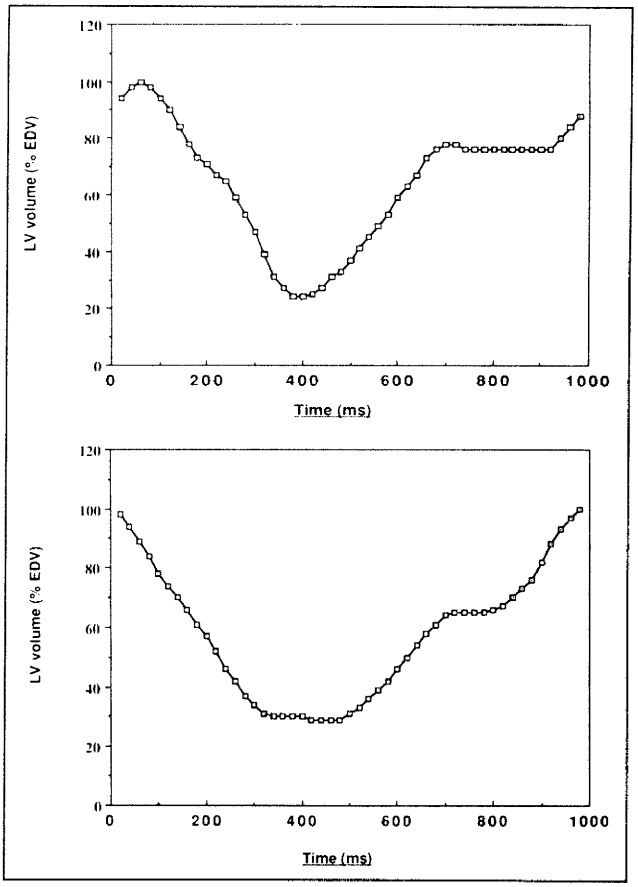


**FIGURE 1.** Global LV time-activity curves are shown for a normal subject (top) and a patient with systemic sclerosis (below). The two subjects are matched for ejection fraction and heart rate.

**TABLE 2**
Cardiac Function in Patients with Crest Syndrome Variant and in Patients with Diffuse Scleroderma

| Variable | Crest syndrome | Diffuse Scleroderma | p Value |
|---|---|---|---|
| Age | 52 ± 11 | 45 ± 10 | ns |
| Duration of disease (yr) | 23 ± 9 | 12 ± 9 | <0.05 |
| Heart rate | 70 ± 6 | 77 ± 14 | ns |
| LVEF | 69 ± 4 | 63 ± 10* | ns |
| PFR | 3.3 ± 0.9 | 3.5 ± 1.2 | ns |
| TPFR | 188 ± 23 | 166 ± 46 | ns |
| IRP | 113 ± 37 | 137 ± 41* | ns |
| CV-TES | 16.2 ± 7.8 | 14.8 ± 6.5 | ns |
| CV-TPFR | 26.2 ± 14.2* | 29 ± 9.7* | ns |
| 1/3 FF | 24 ± 9 | 25 ± 9 | ns |
| RVEF | 47 ± 7 | 47 ± 6 | ns |
| L/H | 0.55 ± 0.13 | 0.48 ± 0.09 | ns |

* $p < 0.05$ versus normal subjects.
Abbreviations as in Table 1.

group did not reach the significant level in the Crest syndrome group probably because of the small number of patients.

Nine patients (five with Crest syndrome) had normal spirometry, six patients (three with Crest syndrome) had mild, five patients (one with Crest syndrome) had moderate, and four (one with Crest syndrome) had severe restrictive lung disease.

There was no difference in RVEF in the patients with restrictive lung disease compared to the other patients (46% ± 7% versus 48% ± 6%, respectively, p = ns). Although an elevated CV-TPFR was found in the Crest syndrome group (Table 2), when the patients were subgrouped according to spirometry results the patients with Crest syndrome variant and restrictive lung disease showed higher CV-TPFR than the normal subjects and the patients without restrictive lung disease (Table 3). On the other hand, CV-TPFR was elevated in patients with diffuse scleroderma either with or without restrictive lung disease (Table 4).

## DISCUSSION

The present study reports the findings in 24 patients with systemic sclerosis studied with rest radionuclide angiography. Prolonged IRP, increased diastolic asynchrony, and reduced first third filling fraction were found in these patients, suggesting the presence of impaired relaxation and/or distensibility (*11*).

Cardiac involvement in systemic sclerosis has been related to the development of myocardial fibrosis. Although the pathogenesis of fibrosis is still under debate, it has been suggested that a reversible vasospastic abnormality in small coronary artery resulted in myocardial fibrosis (*12*). Fibrosis in turn could lead to diminished distensibility (*11*) and increased nonuniformity. Moreover, both relaxation and distensibility are also influenced by temporal and spatial nonuniformity of contraction and relaxation (*13*).

Alterations in diastolic function, including nonuniformity of relaxation and filling, are not only the consequence of fibrosis, but could also be related to a reversible phenomenon such as ischemia. In fact, it has been reported that in many patients with coronary artery disease, preserved rest systolic function, and without previous myocardial infarction, there is regional asynchrony during the diastolic filling phase at rest (*13*). This phenomenon can be related to subclinical myocardial ischemia and/or the presence of regional fibrosis (*13*). However, the latter factor should contribute to a lesser extent, since those diastolic abnormalities could improve after coronary angioplasty (*14*).

The findings of LV diastolic abnormalities in patients

**TABLE 3**
Cardiac Function and Restrictive Lung Disease (RLD) in Patients with the Crest Syndrome

| Variable | Present RLD | Absent RLD | p Value |
|---|---|---|---|
| Age | 55 ± 10 | 48 ± 11 | ns |
| Duration of disease (yr) | 23 ± 7 | 22 ± 11 | ns |
| Heart rate | 72 ± 4 | 67 ± 8 | ns |
| LVEF | 71 ± 4 | 65 ± 5 | ns |
| PFR | 3.4 ± 1.1 | 3.2 ± 0.7 | ns |
| TPFR | 192 ± 23 | 184 ± 26 | ns |
| IRP | 100 ± 53 | 120 ± 28 | ns |
| CV-TES | 20.3 ± 5.3 | 12 ± 8.1 | ns |
| CV-TPFR | 36.3 ± 12.3* | 16.2 ± 6.6 | <0.05 |
| 1/3 FF | 21 ± 11 | 27 ± 6 | ns |
| RFEV | 47 ± 7 | 47 ± 7 | ns |
| L/H | 0.60 ± 0.17 | 0.50 ± 0.05 | ns |

* $p < 0.05$ versus control group.
Abbreviations as in Table 1.

**TABLE 4**
Cardiac Function and Restrictive Lung Disease (RLD) in Patients with Diffuse Scleroderma

| Variable | Present RLD | Absent RLD | p Value |
|---|---|---|---|
| Age | 42 ± 11 | 51 ± 4 | ns |
| Duration of disease (yr) | 10 ± 9 | 15 ± 8 | ns |
| Heart rate | 80 ± 12 | 70 ± 16 | ns |
| LVEF | 64 ± 8 | 61 ± 14 | ns |
| PFR | 3.9 ± 1.3 | 2.7 ± 0.7 | ns |
| TPFR | 160 ± 42 | 180 ± 59 | ns |
| IRP | 120 ± 40 | 170 ± 14 | ns |
| CV-TES | 10.9 ± 5 | 17.7 ± 3 | <0.05 |
| CV-TPFR | 27.4 ± 10.6* | 33.2 ± 6.1* | ns |
| 1/3 FF | 22 ± 9 | 31 ± 6 | ns |
| RVEF | 48 ± 6 | 45 ± 8 | ns |
| L/H | 0.47 ± 0.1 | 0.52 ± 0.05 | ns |

* $p < 0.05$ versus control group.
Abbreviations as in Table 1.

with systemic sclerosis could be due to the presence of myocardial fibrosis. However, it cannot be excluded that myocardial ischemia could contribute to these diastolic abnormalities, since reversible perfusion defects and systolic dysfunction have been reported in patients with systemic sclerosis (*1,15,16*). Whether the alterations in relaxation and uniformity found in this study result from fibrosis or myocardial ischemia or from both cannot be said from our data. However, impaired relaxation may contribute to the evolution of cardiac involvement in systemic sclerosis by worsening regional perfusion (*17*) or by increasing cardiac filling pressure and pulmonary vascular congestion (*17*).

A reduced filling fraction at one-third of diastole was found in systemic sclerosis patients. This finding suggests that a larger amount of filling occurs during atrial systole. We cannot measure the atrial contribution to filling because our data were acquired using the multiple-gated acquisition method. This technique produces a distortion of the final part of the LV volume curve, although a gate tolerance of 5% was used in the present study in order to minimize this effect.

A somewhat intriguing finding was the normal mean value of PFR in the systemic sclerosis group, although 38% of the patients had a subnormal PFR. It has been demonstrated that increasing impairment in relaxation (expressed as isovolumic relaxation time constant) correlates with decreased peak early filling velocity, decreased early diastolic filling, and increased atrial contribution (*18*). In the present study, we did find a decreased early diastolic filling (since the first third filling fraction was lower than normal) and an increased isovolumic relaxation period, but the mean value of PFR was similar in the patient and control groups. A possible explanation of this finding could be an increased atrioventricular pressure gradient producing an increased PFR despite an impaired relaxation (*19*). Since none of the patients included in this study underwent cardiac catheterization, we do not have data on left atrial and ventricular pressure. However, we found a significant positive correlation between the lung-to-heart ratio (an index of pulmonary blood volume) and PFR. From these data we may hypothesize that many of the patients with systemic sclerosis included in this study could indeed have an elevated left atrial pressure and such an increase produces the observed "normal" PFR.

It has been reported (*20*) that cardiac manifestations of the Crest syndrome are distinct from those found in diffuse scleroderma. We did not find any significant difference between patients with the Crest syndrome variant and other patients, although there was a trend toward a higher LVEF in the former group, and the patients with diffuse scleroderma had a LVEF lower than normal subjects. However, while diastolic asynchrony was increased in all patients with diffuse scleroderma, only the patients with restrictive lung disease in the Crest syndrome group showed an elevated CV-TPFR.

There is evidence that different mechanisms produce cardiac involvement in diffuse scleroderma and in Crest syndrome variant. Ellis et al. (*15*) reported that cold-induced left ventricular wall motion abnormalities occurred in 64% of the patients with diffuse scleroderma and in only 20% of the patients with the Crest syndrome. Follansbee et al. (*20*) found that patients with Crest syndrome did not have exercise-induced perfusion defects but only small fixed ones. These reports suggest that in diffuse scleroderma cardiac involvement is more frequent and probably related to an abnormality of coronary circulation at the level of the intramyocardial vasculature (a "myocardial Raynaud's phenomenon") (*1,12,20*), while in the Crest syndrome it is less likely and probably related to the development of myocardial fibrosis. The subtle abnormalities of LV diastolic function (i.e., the increased diastolic asynchrony) we found in the group of patients with Crest syndrome seems to be related to the presence of pulmonary disease. Whether these two phenomenon are only a concomitant expression of the disease or one produces the other cannot be answered from our data. However, the impairment of diastolic function could increase pulmonary vascular congestion and thus also lead to abnormalities in RV function, which in turn may further compromise LV function (*20*).

## ACKNOWLEDGMENT

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# SELF-STUDY TEST
# Gastrointestinal Nuclear Medicine Questions

Questions are taken from the *Nuclear Medicine Self-Study Program I*, published by The Society of Nuclear Medicine

**DIRECTIONS**

The following items consist of a heading followed by numbered options related to that heading. Select those options you think are true and those that you think are false. Answers may be found on page 126.

A gastric emptying study is performed with anterior images only (Fig. 1) with a meal consisting of 300 ml of water and a fried egg sandwich (two pieces of toast and two eggs scrambled and then cooked with 300 $\mu$Ci of $^{99m}$Tc sulfur colloid). (Normal mean [± SD] $T_{1/2}$ = 88 [± 16] min.)

The early and late regions of interest for the total stomach are indicated by the solid lines in Figure 1 and the gastric emptying curve generated is shown in Figure 2.

True statements concerning the results of this study include which of the following?

1. A "lag phase" abnormality is present.
2. Overlap of small bowel activity with the gastric region of interest has significantly prolonged the $T_{1/2}$ of gastric emptying.
3. The solid emptying curve has an exponential emptying pattern after trituration, as expected.
4. The quantitative results shown in the curve (Fig. 2) are artifactual.

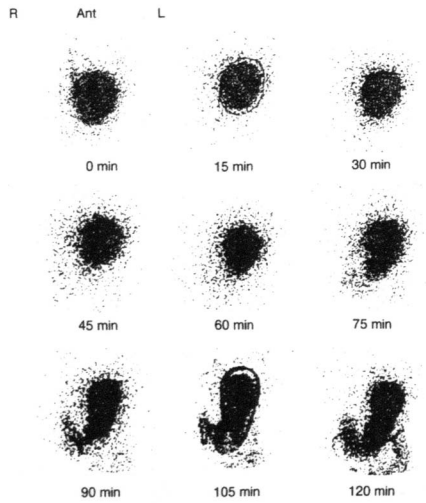


**FIGURE 1**

True statements concerning gastroparesis include which of the following?

5. Gastroparesis can develop acutely in patients without evidence of systemic disease or prior history of a gastrointestinal disorder.
6. Tachygastria (an antral pacemaker that fires at an increased rate) induces gastric stasis.
7. It is usually possible, on clinical grounds, to differentiate patients with idiopathic gastroparesis from those with psychogenic vomiting.
8. Evidence of gastric stasis is present in less than 10% of patients with systemic sclerosis (scleroderma).
9. The surgical techniques used in fundoplication for hiatal hernia and reflux exophagitis prevent the development of gastroparesis.

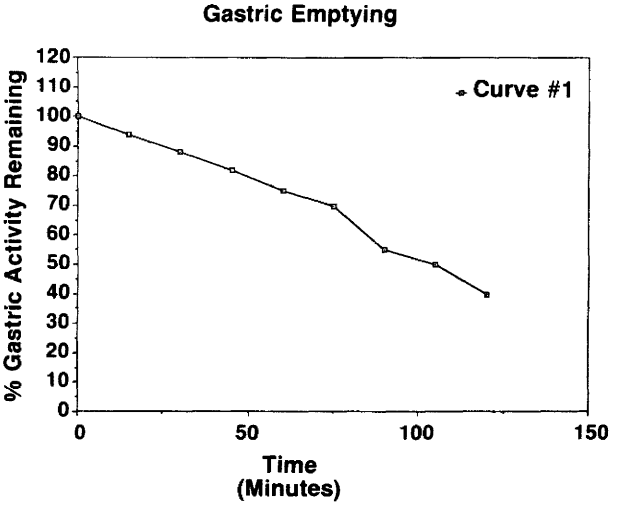


**FIGURE 2**

*(continued on page 126)*