Effect of Systemic Sclerosis on Left Ventricular Long-Axis Motion and Left Ventricular Mass Assessed by Magnetic Resonance

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ABSTRACT

The aim of this study was to assess the effect of scleroderma on left ventricular mass and subendocardial function using cardiovascular magnetic resonance (CMR) to determine parameters reflecting early dysfunction from fibrosis. Fifteen patients with a history of scleroderma had left ventricular mass measured with standard techniques and regional subendocardial contractile function assessed using myocardial velocity mapping in the basal short-axis plane with long-axis sensitized velocity mapping. Peak myocardial velocities in systole and diastole were measured to reflect systolic and diastolic function. The variance in the regional myocardial velocity was determined as a parameter of function heterogeneity around the ventricle. The results were compared with 19 healthy volunteers without a history of cardiovascular disease. In 10 patients, pulmonary transfer factor was measured using a single-breath helium dilution technique. The duration of scleroderma correlated with left ventricular mass (r = 0.7, p < 0.05), the coefficient of variation of velocity (r = 0.63, p < 0.05), and inversely with the mean left ventricular diastolic long-axis velocity (r = -0.63, p < 0.05). There was also a correlation between left ventricular diastolic long-axis velocity and the pulmonary transfer factor (r = 0.7, p < 0.05). Trends suggested differences between control subjects and scleroderma patients for mean systolic (64 vs. 49 mm/sec, p = 0.09) and diastolic (90 vs. 72 mm/sec, p = 0.07) velocities, as well as velocity variance (26 vs. 33, p = 0.09). In conclusion, there is a relationship between duration of scleroderma and both left ventricular mass and diastolic function, which may result from increased myocardial fibrosis. Trends suggest absolute differences in functional values with control subjects that reflect impaired diastolic and systolic function, with greater regional heterogeneity that is consistent with nonuniform collagen deposition, but a larger sample size is required

Received October 6, 1999; Accepted December 9, 1999 Address correspondence to Dudley Pennell. to confirm this. CMR should be explored further as a technique for monitoring myocardial involvement in scleroderma noninvasively.

KEY WORDS: Diastolic function; Left ventricular mass; MR; Scleroderma.

INTRODUCTION

Scleroderma is a multisystem connective tissue disease. Skin and joint problems are the earliest and most obvious manifestations; however, cardiac complications are a commonly recognized problem and a significant cause of morbidity (1). These complications are the cause of death in at least 15% of patients (2). Cardiac involvement ranges from asymptomatic electrocardiographic abnormalities such as conduction defects (3) to more serious sequelae such as left ventricular and biventricular failure (4,5), pericarditis, and arrhythmias. Myocardial fibrosis as a result of excess fibroblast activity is the hallmark of cardiac involvement in scleroderma. It is a major factor in the pathogenesis of cardiac abnormalities and it portends a poor prognosis (6). Histologic studies have demonstrated infiltration of myocardial tissues with collagen (7). It is now accepted that the myocardial fibrosis is a phenomenon unrelated to disease in other tissues or epicardial coronary disease (8,9).

Current techniques for monitoring cardiac involvement only detect disease when fibrosis has already occurred. Once myocardial fibrosis is established, no currently available therapy will reverse the process. Therapy that might suppress excessive fibroblast activity in the early phase has significant side effects. Thus, a technique that would provide early detection of fibrotic involvement would enable treatment to be directed toward patients who might benefit, without exposing unaffected patients to potentially toxic medication. Thallium myocardial perfusion scintigraphy has been used to provide prognostic information in scleroderma, but the radiation involved limits its usefulness for sequential studies, especially in the research environment. Cardiovascular magnetic resonance (CMR) may offer an alternative technique that can be freely repeated by examining long-axis ventricular motion and other physiologic parameters that might reflect early fibrosis.

Long-axis motion of the left ventricle, which is a function of subendocardial myocytes, is affected early in left ventricular disease (10,11). During systole, the base of the heart descends toward the apex and elastic energy is stored in the myocardial wall. During diastole, the release of this energy leads to an increase in ventricular volume and a fall in intraventricular pressure, which facilitates early ventricular filling. Myocardial fibrosis in scleroderma will impair the translation of stored energy into long-axis motion of the ventricle and impair early filling, a common marker of diastolic function. Long-axis function is not easy to assess but can be studied using CMR using velocity mapping (12), which encodes velocity of moving structures in the phase of the magnetic resonance signal and provides accurate measurements of velocity that can be displayed using a gray scale. Velocities toward the base are shown as lighter shades of gray and velocities toward the apex as darker shades of gray, with stationary objects mid-gray. The combination of anatomic magnetic resonance imaging and velocity mapping can be used to study regional long-axis velocity of the left ventricle. Using this technique, we demonstrated abnormal diastolic long-axis function in patients with uncomplicated effort angina and patients with myocardial infarction, both of which are also associated with myocardial fibrosis (12). CMR also provides accurate (13) and reproducible (14) measures of left ventricular mass and volumes, and these may also be helpful in the assessment of scleroderma.

The aim of this study therefore was to assess CMR as a technique to measure the effect of scleroderma on left ventricular mass and left ventricular long-axis function.

METHODS

Study Population

Fifteen patients with scleroderma (4 men, 11 women, aged 28-60 yr, mean age 48) were recruited from the Rheumatology Department of the Royal Free Hospital, London. Scleroderma was diagnosed in accordance with the American Rheumatism Association guidelines (15), with a mean disease duration of 7.8 yr and a range of 2-20. Patients with a history of moderate to severe hypertension were excluded, three patients had a short history of mild hypertension (controlled on single therapy), but all were normotensive at the time of the study. Coronary artery disease and valvular heart disease were excluded by history. Vasodilators such as nifedipine were stopped on the day of the study. Steroids were not withheld. The control population for measures of long-axis function consisted of 19 healthy volunteers (11 men, 8 women, aged 33-76, mean age 47) without a history of cardiovascular disease.



Figure 1. (Top) Spin echo image in the left ventricular shortaxis plane, illustrating the anatomy and the plane used for the velocity studies. Velocity map in the short-axis plane in a patient with scleroderma in systole (bottom, left) and diastole (bottom, right). The chest wall is mid-gray, indicating that it is stationary, whereas the myocardial ring (arrow) is a darker shade of gray in systole, indicating motion toward the apex, and lighter in diastole, indicating motion toward the base.

Magnetic Resonance Velocity Mapping

A modified Picker 0.5-T machine was used to acquire cardiac images with a surface receiver coil. Conventional spin echo sequences (echo time, 40 msec) were used to document anatomy and to define the vertical and horizontal long-axis and a basal short-axis plane at end-systole that was below the mitral annulus such that both the septum and lateral wall were muscular throughout the cardiac cycle despite systolic descent of the base toward the apex. Using a cine gradient echo sequence (16), velocity maps were acquired in this plane, as previously described (17) (Fig. 1). Velocity was encoded through the plane, which is parallel to long-axis motion, and the velocity window was set at $\pm 150-250$ mm/sec. All studies were performed using 192 phase encoding steps, each averaged from two repetitions. Field of view was between 350 and 400 mm, giving a pixel size of 1.4×1.8 to 1.6 \times 2.1 mm with 10-mm slice thickness. The first image was acquired 18 msec after the R wave, and temporal resolution was 25 msec, giving 24-31 images per cardiac cycle.

Left Ventricular Mass

Left ventricular mass was measured from contiguous spin echo images of the left ventricle, either acquired as separate end-systolic transverse images (10 patients) or as a multislice acquisition of short-axis slices centered around end-systole (5 patients), as previously described (18). Slice thickness was 1 cm and the area of left ventricular myocardium in each slice was summed to measure volume and hence myocardial mass, assuming a specific gravity of 1.05 (19). Left ventricular mass was normalized to body surface area.

Analysis

Reference and velocity encoded phase images were subtracted to produce velocity maps of long-axis myocardial motion and zero velocity was corrected by manual selection of stationary structures in the chest wall. The endocardial and epicardial boundaries were traced manually. The myocardium was divided into 16 segments, and the mean velocity in each segment was calculated (Fig. 2). Velocity curves for each segment were constructed for the entire cardiac cycle. All 16 segments were then summed to provide a mean long-axis velocity curve for the left ventricle. The peak systolic velocity, V_{syst} , and the peak diastolic velocity, V_{diast} , were measured (Fig. 3).

The variability of regional velocity of the 16 segments at the time of peak early diastolic velocity was used as a marker of homogeneity of myocardial relaxation (Fig. 3), expressed as the coefficient of variation (V_{var}) :

Coefficient of variation =

$$\frac{\text{standard deviation of velocity}}{\text{mean velocity}} \times 100\%$$

Lung Function

Transfer factor was measured in 10 patients, using the single-breath helium dilution method with 0.28% carbon monoxide.

RESULTS

Left Ventricular Mass

Mean left ventricular mass index (\pm SD) was 93 \pm 22.9 gm⁻² which was not different from our control population (17 men, 119 \pm 17 gm⁻², 10 women, 91 \pm 15 gm⁻², age range 16–64). Left ventricular mass correlated positively with the duration of disease (r = 0.7, p < 0.01; Fig. 4). There was no significant correlation between left ventricular mass index and age.

Karwatowski et al.



Figure 2. The velocity map through a basal short-axis plane of the left ventricle (see Fig. 1) is divided into 16 segments. The mean velocity of each segment can then be plotted through the cardiac cycle as displayed in Fig. 3.

Left Ventricular Long-Axis Wall Motion

One patient became claustrophobic after the left ventricular mass study and did not undergo velocity mapping. Two other patients were excluded: one had a sinus tachycardia of 130 and the other had left bundle branch block. This was because both patients would have produced abnormal ventricular wall motion in their own right.

Comparison with Control Subjects

Magnetic resonance long-axis velocity measurements for the two groups are in given Table 1. In the sclero-



Figure 3. Regional left ventricular long-axis wall velocity through the cardiac cycle for 4 of the 16 segments in an individual subject. During systole, the base of the heart descends toward the apex, storing energy in elastic elements of the myocardium. During early diastole, there is rapid motion of the base away from the apex as this energy is released. The mean of all segments was taken to calculate the peak systolic and diastolic velocities. At the time of the peak diastolic velocity, the coefficient of variation was calculated as a measure of homogeneity of relaxation.





Figure 4. Correlation of duration of disease and left ventricular (LV) mass. Solid line, mean; dashed lines, ± 2 SD for a female control population.

derma group there was a trend for mean systolic (p = 0.09) and diastolic (p = 0.07) velocity to be lower than the control group. There was also a trend for V_{var} (p = 0.09) to be greater in the scleroderma patients than in the control group. There was no relationship between systolic and diastolic long-axis velocities in the scleroderma group (r = -0.09, p = 0.79).

Relation to Duration of Disease

The duration of disease correlated with mean diastolic velocity (Fig. 5) and with V_{var} but not with mean systolic velocity. There was no significant correlation between

Table 1

Comparison of Magnetic Resonance Measures of Systolic and Diastolic Long-Axis Velocity

<u></u>	Control Subjects (n = 19)	Scleroderma $(n = 12)$	р
Age (vr)	47.3 ± 11.5	47.2 ± 10.0	0.98
Systolic velocity (mms ⁻¹)	64.1 ± 17.1	49.3 ± 18.6	0.09
Diastolic velocity (mms ⁻¹)	90.0 ± 24.8	72.2 ± 27.2	0.07
V _{Var}	25.8 ± 8.8	33.2 ± 15.2	0.09

Values are means \pm SD. p is the result of an unpaired Student's t-test. V_{var} , variability of regional velocity of the 16 segments at the time of peak early diastolic velocity, a marker of homogeneity of myocardial relaxation, expressed as the coefficient of variation.





Figure 5. Correlation of duration of disease and mean early diastolic long-axis velocity (V_{mean}).

systolic velocity, diastolic velocity or V_{var} , and age. The correlations between measures of long-axis motion and ventricular mass with duration of disease and age are given in Table 2.

Transfer Factor

There was a correlation between gas transfer and mean diastolic velocity (r = 0.7, p < 0.05), but there was no correlation between length of disease and transfer factor.

DISCUSSION

Cardiac involvement in scleroderma causes myocardial fibrosis, which could potentially alter both ventricu-

Table 2

Spearman Correlation Coefficient for Relationship Between Measures of Long-Axis Motion and Ventricular Mass with Duration of Disease and Age

	Duration of Disease	Age (vr)
	0.35 (0.20)	
V _{syst}	0.35 (p = 0.29) -0.63 ($p \le 0.05$)	-0.28 (p = 0.37) -0.31 (p = 0.33)
V diast Vvar	$0.63 \ (p < 0.05)$ $0.63 \ (p < 0.05)$	$0.23 \ (p = 0.44)$
LV mass index	$0.7 \ (p < 0.01)$	$0.09 \ (p = 0.76)$

 V_{xyst} , peak systolic velocity; V_{diast} , peak diastolic velocity; V_{var} , variability of regional velocity of the 16 segments at the time of peak early diastolic velocity, a marker of homogeneity of myocardial relaxation, expressed as the coefficient of variation; LV mass index, left ventricular mass standardized to body surface area.

lar wall motion and myocardial mass. The degree of impairment of ventricular function has been related to the degree of fibrosis (20). Ventricular filling has been used as a measure of diastolic function, and abnormalities have been detected associated with hand grip stress (21); however, there are no published studies of diastolic myocardial long-axis motion.

Myocardial Long-Axis Velocity

The value of studying long-axis wall motion as a marker of subendocardial function comes from theoretic and practical considerations. During systole, energy is stored in the elastic elements of the myocardium. The amount of energy stored depends on the systolic function of the ventricle (22,23). This energy is released when the actin-myosin cross-bridges are uncoupled during early diastole (24), initiating long-axis motion of the ventricle (25), and in normal subjects this results in a negative intraventricular pressure during early diastole (26). This drop in pressure will increase the atrioventricular pressure gradient, augmenting peak early filling, a common marker of diastolic function (27,28). Myocardial fibrosis, by its effect on chamber compliance, will impair the conversion of stored elastic energy into wall motion, and thus it will impair early ventricular filling (29). Assessment of diastolic function by echocardiography has centered around measurement of transmitral blood flow velocity. This is a function of left atrial filling pressure and ventricular wall motion. Pseudo-normalization of filling patterns due to raised atrial pressure can occur and mask abnormal myocardial relaxation (30). Assessment of the underlying pattern of wall motion by magnetic resonance might offer a more sensitive measure of ventricular function.

In this study, our results suggest that diastolic myocardial velocities are lower in patients with scleroderma than control subjects, although this finding just failed to reach statistical significance. However, there was a significant inverse relation between the duration of disease and the diastolic myocardial velocity, suggesting that diastolic dysfunction advances with longevity of disease. The absolute values of myocardial velocity versus control may have become significant, therefore, if the sample size had been larger. Although the patients with scleroderma also had lower systolic velocities than control subjects, if impaired systolic function was the underlying reason for the impaired diastolic function, then we would expect to see a relationship between systolic velocity and disease duration, but this was not found. The impaired diastolic function we observed, although affected by systolic dysfunction, is therefore likely to be the result of a primary diastolic abnormality, the most likely cause being the presence of increased myocardial fibrosis impairing the transition of stored energy to long-axis wall motion. Because the patients were asymptomatic from the cardiovascular perspective, the implication is that such myocardial fibrosis is clinically silent. The heterogeneity of myocardial velocities in the scleroderma group was likewise close to statistical significance in being greater than in normal subjects. This parameter reflects variations in regional function, and is likely to have greater variability if fibrosis from scleroderma were laid down in a patchy fashion. This finding would therefore accord with pathologic studies (7).

Left Ventricular Mass

Both postmortem and clinical studies have demonstrated increased left ventricular wall thickness (31) and mass (32,33) in scleroderma, and these changes are associated with impaired left ventricular filling (34). The clinical studies have used echocardiography to measure left ventricular mass. CMR may have advantages in that unlike echocardiography it makes no assumptions about ventricular geometry. However, we did not find a significant difference in left ventricular mass between control subjects and patients with scleroderma, and this may relate to the limited number of patients in our study. We have shown that left ventricular mass increases with the duration of disease, and this may be true either of myocardial hypertrophy or infiltration with fibrous tissue. We have assumed a specific gravity for myocardium of 1.05 for all patients, but this will vary in patients depending on the degree of fibrosis. Without knowing the exact extent of fibrosis, which is not possible antemortem, the exact specific gravity cannot be known and so we have elected to use the same figure for all patients and control subjects. Hypertension is a possible mechanism of hypertrophy, but no patient was hypertensive at the time of the study, although three patients had a history of mild hypertension. Previous studies have not demonstrated a relationship between the duration of disease and either left ventricular mass or diastolic indices (33), but this was demonstrated in our study. Our patient population had a longer duration of disease, and this in conjunction with a potentially more accurate measure of left ventricular mass may have allowed the association to become apparent.

Underlying Mechanisms

Scleroderma is characterized by an excessive deposition of collagen in all involved organs due to an overproCMR of Ventricular Function in Scleroderma

duction of extracellular matrix after induction of gene expression. The structure of the collagen produced is normal but is present in greater amounts (35). A close interaction between inflammatory cells and fibroblasts is required for the initial activation of fibroblasts (36). Plasma endothelin 1, a potent vasoconstrictor and a fibroblast mitogen, is raised in systemic sclerosis (37) and may contribute to the vasospasm and increased collagen synthesis (38) as well as Raynaud's phenomenon (39). Endothelin-binding receptor density is significantly higher in patients with scleroderma compared with control subjects (40). Free radicals may also play a role in the fibrosis (34).

Pulmonary Function

Pulmonary involvement is an important cause of morbidity (41) and mortality (42,43) in scleroderma, and a restrictive defect with radiographic evidence of interstitial fibrosis is the most common finding. The fibrosis involves the alveolar septa, the bronchial walls, and the interstitium of the lung, ultimately leading to loss of capillaries and alveolar spaces (32,44,45). Gas transfer correlates with the degree of lung involvement as quantified by computed tomography (46). The relationship, if any, between cardiac and respiratory involvement is unknown. If involvement of the two organs is related, possibly as a function of duration of disease, this would explain the association we observed between diastolic left ventricular function and pulmonary function; however, if that was the case, then one would have expected a relationship between duration of disease and lung function that we did not find.

Future Applications

To treat patients early in their disease, cardiac or pulmonary involvement must be detected before irreversible damage has occurred. Abnormalities of diastolic function are the earliest marker of disease, and further evidence of subclinical involvement might come from studies coupled with stress. CMR can accurately measure ventricular mass and can also provide sensitive measures of ventricular function. This could find application in the long-term follow-up of patients. The technique continues to evolve with faster sequences and improved image quality, and this will improve the assessment of diastolic function. Recent advances in sequence design have brought the possibility of imaging the lung parenchyma (47). The combination of the ability to make sensitive measures of ventricular function and pulmonary involvement would give magnetic resonance a significant benefit over other imaging modalities.

We conclude therefore that left ventricular mass increases and diastolic function is impaired in scleroderma and that abnormalities detected by CMR are related to the duration of disease. Further studies of cardiac and possibly pulmonary involvement are needed to assess its place in the management of CMR in these patients.

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