Myocardial gallium-67 citrate scintigraphy in patients with systemic sclerosis

J Gaál, I Hegedüs, K Dévényi, L Czirják

Abstract

Objective—To detect myocardial involvement in 16 patients with systemic sclerosis using radiogallium scintigraphy

Methods—Sixteen patients with systemic sclerosis were investigated by myocardial gallium-67 citrate scintigraphy. Echocardiographic studies and (in the positive cases) magnetic resonance imaging were also performed.

Results—Increased myocardial gallium uptake was found in five of the 16 patients. None of these positive cases exhibited any ‘classical’ clinical, electrocardiographic or laboratory signs characteristic of myocarditis. The mean age of the positive cases was 60.8 (SD 5.0) years compared with 44.6 (10.7) years for the negative cases; no difference was detected in the mean disease duration between these two groups. Two of the affected cases belonged to the limited scleroderma subgroup.

Conclusions—In spite of the low number of patients investigated, it is tempting to speculate that elderly patients with a disease onset around 60 years tend to be the candidates in whom a positive gallium-67 scintigraphy test may best indicate a silent myocardial interstitial inflammation.

(Ann Rheum Dis 1995; 54: 856–858)

Several forms of heart involvement can be detected in systemic sclerosis (SSc), including pericarditis, myocardial fibrosis, disturbances of the conduction system, impaired left ventricular systolic or diastolic function, left ventricular wall motion abnormalities, and primary or secondary pulmonary hypertension. Myocarditis is rare, but occasionally present in this disorder. As an extremely rare finding, acute myocarditis with well detectable clinical symptoms and laboratory findings has also been described in SSc. The majority of cases of myocarditis seem to be associated with skeletal myopathy.

Gallium-67 is a ferric ion analogue successfully used as an inflammatory avid radiosotope in routine screening for acute and chronic inflammatory states, with a sensitivity of about 90%. In particular, a positive gallium-67 scan usually correlates with the presence of inflammatory cells in endomyocardial biopsy specimens, participating in autoimmune myocardial destruction.

Patients and methods

PATIENTS

Sixteen hospital inpatients who fulfilled the diagnostic criteria for SSc were randomly selected for the study. Their clinical and laboratory data were evaluated by a standard procedure, and revealed 12 of them to have some cardiac symptoms in their history (table). Five patients showed a pericardial thickening indicating an earlier pericarditis. Nine had retrosternal chest pain characteristic of angina pectoris in their case history. Signs of ischaemia were detected on the resting electrocardiogram (ECG) in two of these patients and during the stress test by bicycle ergometer in another. Of the six remaining patients, three did not show any ECG abnormality during exercise, while this investigation was not performed for the other three because of muscle weakness, polyarthritis, or both.

Clinical data of the 16 patients with systemic sclerosis

<table>
<thead>
<tr>
<th>Pt</th>
<th>67Ga uptake (grade)</th>
<th>Age at onset (yr)</th>
<th>Disease duration (yr)</th>
<th>Sex</th>
<th>Manifestation</th>
<th>Heart symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>FZ</td>
<td>–</td>
<td>60</td>
<td>29</td>
<td>F</td>
<td>T, O, P, L</td>
<td>A, ST</td>
</tr>
<tr>
<td>GE</td>
<td>–</td>
<td>44</td>
<td>14</td>
<td>F</td>
<td>T, H, O, P, D</td>
<td>A</td>
</tr>
<tr>
<td>JE</td>
<td>–</td>
<td>38</td>
<td>6</td>
<td>F</td>
<td>T, H, O, P, D</td>
<td>A</td>
</tr>
<tr>
<td>JF</td>
<td>–</td>
<td>49</td>
<td>21</td>
<td>F</td>
<td>T, O, P, T, D</td>
<td>A</td>
</tr>
<tr>
<td>PA</td>
<td>–</td>
<td>56</td>
<td>1</td>
<td>F</td>
<td>H, P, T, L</td>
<td>A</td>
</tr>
<tr>
<td>SJ</td>
<td>–</td>
<td>38</td>
<td>5</td>
<td>F</td>
<td>T, O, M, P, L</td>
<td>A</td>
</tr>
<tr>
<td>PJ</td>
<td>–</td>
<td>61</td>
<td>8</td>
<td>F</td>
<td>T, M, P, L</td>
<td>A</td>
</tr>
<tr>
<td>Sz</td>
<td>–</td>
<td>38</td>
<td>5</td>
<td>F</td>
<td>T, O, M, P, L</td>
<td>A</td>
</tr>
<tr>
<td>Cd</td>
<td>–</td>
<td>44</td>
<td>3</td>
<td>F</td>
<td>T, P, T, L</td>
<td>A</td>
</tr>
<tr>
<td>MJ</td>
<td>–</td>
<td>28</td>
<td>7</td>
<td>F</td>
<td>T, H, O, P, T, L</td>
<td>Pe</td>
</tr>
<tr>
<td>KS</td>
<td>–</td>
<td>35</td>
<td>4</td>
<td>F</td>
<td>T, H, P, T, D</td>
<td>Pe</td>
</tr>
<tr>
<td>ZJ</td>
<td>++</td>
<td>65</td>
<td>4</td>
<td>M</td>
<td>T, H, T, D</td>
<td>A</td>
</tr>
<tr>
<td>SE</td>
<td>+++</td>
<td>62</td>
<td>4</td>
<td>F</td>
<td>T, H, O, P, T, D</td>
<td>A, Pe, V</td>
</tr>
<tr>
<td>SK</td>
<td>+++</td>
<td>65</td>
<td>5</td>
<td>F</td>
<td>T, H, O, P, T, D</td>
<td>A, Pe, V</td>
</tr>
<tr>
<td>SJ</td>
<td>+++</td>
<td>59</td>
<td>3</td>
<td>F</td>
<td>T, O, P, L</td>
<td>A</td>
</tr>
<tr>
<td>BB</td>
<td>+++</td>
<td>53</td>
<td>16</td>
<td>F</td>
<td>T, H, O, C, P, A, L, L</td>
<td>ST</td>
</tr>
</tbody>
</table>

Manifestations: T = Telangiectasia; O = oesophageal involvement; P = pulmonary involvement; L = Limited cutaneous systemic sclerosis; H = skin hypo- and/or hyperpigmentation; D = diffuse cutaneous systemic sclerosis; TP = antitopoisomerase 1 antibody positivity; M = myositis; C = calcinosis; AC = anticientromere antibody.

Heart symptoms: A = angina pectoris in case history; ST = supraventricular paroxysmal tachycardia; Pe = pericarditis in case history; V = ventricular extrasystolia.

GALLIUM-67 IMAGING OF THE HEART

Gallium-67 imaging was performed 72 hours after the intravenous administration of 200 MBq 67Ga-citrate (Atomki, Debrecen, Hungary). Images were taken using a large field of view gamma camera (MB-9200, Gamma Mueck, Hungary), equipped with a medium energy, parallel hole collimator. For the first patient, single channel acquisition was used (185 keV ± 20%), and images were acquired until either 15 minutes or 400,000 counts had elapsed; the procedure was later changed to two channel acquisition (185 keV ± 20% and 93 keV ± 15%), resulting in much higher count rates, and thus allowing for better statistics.
and shorter acquisition time (12 minutes or 1 million counts). Images (128 × 128) were stored and evaluated using a dedicated computer system (DIAG). Both raw and Metz filtered images were displayed, and the intensity of gallium uptake in the projection of the heart was compared with that of the sternum.

Evaluation of the isotope uptake by the myocardium was performed by an assessor blind to the clinical or laboratory details of the particular patient. The images were graded on a scale of 1 to 4 where 1 = no definable or barely perceptible activity over the myocardium; 2 = definite myocardial visualisation but decisively less intense than in the sternal area; 3 = myocardial activity almost equal to that of sternum; and 4 = myocardial activity greater than that of the sternum. Patients who had gallium-67 uptake of grade 2 were considered to be weakly positive, while those who had grade 3 or 4 were considered as unequivocally positive.

Eighteen age matched patients without any evidence of cardiac disease were evaluated as controls. The clinical diagnoses of this group were osteomyelitis, sarcoidosis, gluteal abscess, femoral head necrosis, chronic cholecystitis, splenic abscess, tumour of the caecum, Burkitt’s lymphoma, and periappendicular abscess (one case each). In addition, four patients with fever of unknown origin, and five patients with Hodgkin’s disease were also investigated as controls. All the control patients showed an insignificant or no uptake of gallium-67 (grade 1) (figure), apart from one who exhibited a grade 2 uptake.

**ECHOCARDIOGRAPHIC STUDIES**

All patients underwent echocardiography at the same investigation, as described previously. Those exhibiting signs of pericarditis were excluded from the study.

**MAGNETIC RESONANCE IMAGING (MRI)**

Patients with a positive gallium uptake were also investigated by MRI (Shimadzu SMT 100X, Japan) (1 tesla) to exclude the presence of enlargement of the mediastinal lymph nodes and pericarditis. The examinations were performed with the subject in the supine position, using a body coil. Cardiac gating was used to accommodate for motion, and pulsation artefacts. The scans were performed at a 10 mm slice thickness with section width 10 mm also. Axial and coronal scans were performed from the thoracic outlet to the diaphragmatic region, by T1 and T2 weighted imaging. No contrast material was used. Fewer than 21 days elapsed between the gallium imaging and the MRI.

**Results**

Five patients with SSc showed an increased cardiac gallium-67 uptake. In four of them the scans were interpreted as unequivocally positive (intensity nearly equal to that of the sternum) (figure), while the remaining patient exhibited a weakly positive scan (grade 2) (table).

Three of the uptake positive patients belonged to the diffuse scleroderma subset (table). The mean follow up times of the positive and negative cases were similar. Patients showing an increased uptake of gallium-67 were considerably older than the other patients (60-8 (SD 5-0) versus 44-6 (10-7) years, respectively; p < 0-007 by t test), but no difference was found between the two groups in the mean disease duration. The age of onset of disease in patients showing a positive gallium-67 scan was 54±6 (9-5) years, compared with 35±3 (10-4) in the negative cases. The extent of skin involvement was similar in the positive and negative groups (data not shown). None in the positive group had myositis (table).

There were no increased concentrations of creatine kinase MB or lactate dehydrogenase (LDH) isoenzyme, and no clinical or ECG findings characteristic of myocarditis in the uptake positive patients, and no signs of pericarditis were detected by echocardiography. Furthermore, parameters of systolic and diastolic function (including the end diastolic and end systolic volume, ejection fraction, fractional shortening, and isometric relaxation time) were not different in patients with positive gallium scintigraphy compared with the remaining patients. The E:A ratio (a diastolic parameter calculated from two characteristic waves of the mitral Doppler curve, named E and A) was also similar in these two groups of patients (data not shown).

The magnetic resonance imaging also performed in the five positive patients revealed no
signs of enlarged mediastinal lymph nodes of pericarditis as potential causes of the positivity of isotope uptake.

Discussion
Myocarditis with the ‘classic’ ECG, echocardiographic findings, and increased creatinine kinase MB or LDH isoenzyme concentrations is a rare finding in patients with SSC.4 5 7 The prevalence of myocardial fibrosis can reach 81%,2 and this high proportion of cases with fibrosis may not be fully explained by the secondary consequences of myocardial ischaemia caused by episodic vasospasm or vascular abnormalities of the heart in SSC.15

The initiating events in SSC are characterised by inflammatory signs involving T lymphocytes and monocytes-macrophages in both the skin and lung involvements of the disease. It is tempting to speculate that the early myocardial involvement is also accompanied by inflammatory signs.

A simple and reliable method for the detection of a silent myocardial inflammation remains lacking. Endomyocardial biopsying is highly specific, but its sensitivity is questionable because inflammation may be focal or patchy, and thus missed. The need for a special centre with trained personnel and the potential risks involved in the investigation are further disadvantages of this method. Myocardial gallium-67 citrate scintigraphy as a simple non-invasive method for the possible detection of cardiac inflammation may have a considerable value in the diagnosis of myocarditis.10 11 It is possible that the increased gallium uptake in our five positive patients may have reflected a chronic interstitial inflammation of the myocardium. Speculation that increased cardiac radiogallium uptake is a possible indicator of myocardial involvement requires confirmation in complementary endomyocardial biopsy specimens.

Although the number of patients we studied was small, it is tempting also to speculate that elderly patients with a disease onset around the age of 60 years are likely to be the candidates of choice for detection of silent myocardial interstitial inflammation by means of gallium-67 scintigraphy. One contributing factor leading to poor prognosis in elderly patients with SSC15 may be the silent myocardial interstitial inflammation which can be present in both the diffuse and the limited scleroderma subsets.

We acknowledge with gratitude the valuable advice, help, and cooperation of Jozsef Varga PhD.