^{111}Indium antimyosin antibody imaging of primary myocardial invovement in systemic diseases

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Abstract

***Objective*—The diagnosis of primary myocardial involvement in systemic diseases is clinically relevant but difficult in the absence of specific criteria. Whatever the underlying disease, myocytes degeneration is observed during the active phase of myocardial damage. The aim of this study was to assess the diagnostic value of scintigraphic imaging with ^{111}Indium antimyosin antibody (AM), a specific marker of the damaged myocyte, for ongoing myocardial damage related to systemic diseases.**

***Methods*—40 patients with histologically confirmed systemic diseases were studied. They were classified into two groups according to the presence (group 1, n=30), or the absence (group 2, n=10) of clinical, electrocardiographic (ECG) or echocardiographic signs suggestive of myocardial involvement. Planar and tomographic acquisitions were obtained 48 hours after injection of AM (90 MBq). Rest ^{201}thallium (Tl) scintigraphy was also performed to assess myocardial perfusion and scarring. Clinical, ECG, and echocardiographic ± scintigraphic evaluations were repeated during follow up (17 ±19 months) in 36 of 40 patients.**

***Results*—In group 1, 13 of 30 patients (43%) showed diffuse significant AM uptake throughout the left ventricle (LV), and no or mild Tl abnormality. Two of these were asymptomatic, four had normal ECG, and two had no clinical or echographic LV dysfunction. All patients in group 2 had negative AMA scintigraphy and normal Tl scintigraphy. During follow up of 12 AM positive patients, cardiac status improved after immunosuppressive treatment was intensified in nine cases, worsened in two cases, and remained stable in one. During follow up of 24 AM negative patients, cardiac status remained stable in 23 cases despite treatment not being increased in 20, including two patients with sequellary myocardial involvement. The last patient developed mild LV dysfunction after 36 months.**

***Conclusion*—AM scintigraphy allows detection of active myocardial damage related to systemic diseases, with increased specificity compared with conventional methods, and increased sensitivity in some cases. Further studies are needed to assess the potential value of AM scintigraphy as a therapeutic guide.**

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Primary cardiac involvement in systemic diseases carries a poor prognosis and has important therapeutic implications.[1] Both the recognition of myocardial involvement, and the discrimination between active and sequellar myocardial damage are relevant for the therapeutic decision. But the diagnosis may be difficult in the absence of specific criteria. Histological confirmation can be invasively obtained by endomyocardial biopsy, but with a poor sensitivity because of the patchy involvement of the myocardium.[2–4] Clinical, electrocardiographic (ECG), echocardiographic, electrophysiological, and angiographic features are not specific for cardiac involvement, and their precise diagnostic value has not been determined.

Whatever the underlying systemic disease, primary myocardial injury always leads to focal myocyte degeneration with subsequent fibrosis, either because of a direct inflammatory process or because of myocardial ischaemia secondary to injury of the microvessels or, more rarely, of the epicardial coronary arteries.[1] Necrosed myocytes are present only during the active phase of myocardial damage. Thus a non-invasive method for detecting ongoing myocytes necrosis may be of interest to assess active myocardial disease. Labelled antimyosin antibodies bind specifically to exposed myosin of myocytes with a damaged cell membrane.[5] The aim of this study was to assess the diagnostic value of ^{111}indium antimyosin antibody (AM) scintigraphy for active myocardial damage related to systemic diseases. Myocardial perfusion and scarring was simultaneously assessed by means of ^{201}thallium (Tl) scintigraphy at rest.

Methods

PATIENTS

We studied 40 patients with histologically confirmed systemic diseases (table 1). All had routine clinical, electrocardiographic, and echocardiographic evaluations, and creatine phosphokinase (CPK) assay. On the basis of this staging, patients were classified into two groups according to the presence (group 1, n=30) or absence (group 2, n=10) of signs suggesting myocardial involvement.

Group 1 (G1) patients

Thirty consecutive patients in G1 were investigated prospectively.

Sixteen of the 30 patients were symptomatic, with left ventricular (LV) failure (n=8), syncope related to atrial flutter (n=1), palpitations related to ventricular premature beats (n=2), chest pain (n=1), or dyspnea not explained by

Table 1 Characteristics of the patients in group 1 and group 2

	Group 1 (n=30)	*Group 2 (n=10)*	
Systemic diseases	8 polymyositis 4 periarteritis nodosa 4 lupus 3 Churg-Strauss syndrome 3 systemic sclerosis 3 dermatopolymyositis 3 sarcoidosis 1 rheumatoid arthritis 1 MCTD	6 polymyositis 2 systemic sclerosis 2 dermatomyositis	
Age	23–73, mean (SD): 47 (15)	19–67, mean (SD): 40 (17)	NS, p=0.25
Sex ratio: men/women	15/15	3/7	
Mean time between diagnosis and inclusion	0–165, mean (SD): 43 (46) months	2–101, mean (SD): 22 (29) months	NS, p=0.18

Group 1: patients with cardiac signs suggesting myocardial involvement. Group 2: patients with no cardiac sign. MCTD: mixed connective tissue disease.

pulmonary dysfunction (n=4). Furthermore, echocardiographic abnormalities were present in 11 of these 16 patients, and arrhythmia or conduction disturbance was present in 10.

Fourteen of the 30 patients were asymptomatic. Myocardial involvement was suspected on the basis of echographic LV dysfunction in four cases, pericardial effusion with no LV dysfunction on echocardiography in three, electrocardiographic changes in six (frequent complex ventricular premature beats in one, first degree atrioventricular block in two, left bundle branch block in one, small R waves in anterior precordial leads in one, ST-T segment abnormalities in one, and CPK-MB increase in one (rheumatoid arthritis).

Globally, when considering the whole group of 30 patients (symptomatic or not): 15 had clinical and/or echographic LV dysfunction, six had pericarditis, and 22 had electrocardiographic abnormalities.

Group 2 (G2) patients

Ten patients with histologically confirmed systemic disease but no clinical, electrocardiographic or echocardiographic signs of myocardial injury (group 2) served as controls.

Table 2 AM scintigraphy results in patients of group 1

Main cardiac abnormality	*Number*	*ECG abnormalities*	*Echographic LV dysfunction*	*AM +*
Symptomatic patients				
APO or sub-APO	8	4/8	8/8	8/8
Syncope (related to atrial flutter)	1	1/1	1/1	1/1
Palpitations (ventricular premature beats)	2	2/2	1*/2	1*/2
Chest pain	1	1/1	0/1	0/1
Dyspnea	4	2/4	1†/4	1†/4
Asymptomatic patients				
Echographic LV dysfunction	4	3/4	4/4	1/4
Pericardial effusion	3	2/3	0/3	0/3
ECG abnormalities	6	6/6	0/6	1/6
CPK-MB increase (31 UI/l, normal values <10)	1	1/1	0/1	0/1
Total	30	22	15	13

APO: acute pulmonary oedema. *LV dysfunction and AMA positivity in the same patient. †LV dysfunction and AMA positivity in two different patients. ECG abnormalities: electrocardiographic abnormalities. CPK-MB: myocardial creatin phosphokinase enzyme.

Table 3 Electrocardiographic and echocardiographic findings with respect to AM scintigraphic results in group 1

	AM positive (n=13)	*AM negative (n=17)*	*p Value*
HLR	2.06 (0.17)	1.45 (0.18)	0.000005
LVFS (%)	23.2 (7.0)	36.3 (5.7)	0.000005
LV diastolic diameter (mm)	57.2 (5.4)	45.4 (5.0)	0.00003
Septal thickness (mm)	11.1 (2.5)	9.6 (1.7)	NS
Posterior wall thickness (mm)	9.5 (2.7)	8.7 (1.9)	NS
Pericarditis	2/13 (15%)	2/17 (12%)	NS
ECG abnormalities	10/13 (77%)	13/17 (76%)	NS

HLR: heart to lung ratio. LV: left ventricular. LVFS: left ventricular fractional shortening. ECG abnormalities: electrocardiographic abnormalities. Data shown as mean (SD) and percentages.

AM SCINTIGRAPHY

AM scintigraphy was performed within three weeks after the discovery of cardiac signs (when present).

Acquisition protocol

Seventy four MBq of AM (Myoscint, Centocor, Mallinckrodt) was injected intravenously. Forty eight hours later, planar thoracic images (anterior, 40° and 70°, oblique anterior views) were acquired with a 20% window centred on the 173 and 247 KeV photopeaks of ^{111}indium, using a 128 × 128 matrix and a preset time of 10 minutes. On the anterior planar image, a heart/lung ratio (HLR) was calculated using two regions of interest, one on the cardiac area, and the other on the right lung. Then 111 MBq of Tl was injected and dual isotope tomographic acquisition (SPECT) was performed with a double headed right angle gammacamera (Sopha DST) fitted with medium energy collimators. Tomographic acquisition parameters were as follows: 180°, circular orbit, 32 projections, matrix 64 × 64, 40 s per projection. The two datasets (Tl-SPECT and ^{111}indium-SPECT) were processed simultaneously, identically and automatically as follows: filtered (hamming), back projection, centred and reoriented along the three axes with the help of the Tl acquisition as landmark. Neither background subtraction nor attenuation correction was used. Corresponding short axis, vertical long axis, and horizontal long axis slices for each SPECT acquisition were displayed simultaneously. If needed, the corresponding slices could be superimposed to better localise AM uptake.

Data analysis

The planar and tomographic scintigrams were scored by two investigators from the Department of Nuclear Medicine, first after each scan, then at the end of the study. A final consensus reading was made in case of disagreement. Intraobserver and interobserver reproducibility was respectively 90% and 85%. AM scintigraphy was scored as normal or abnormal on planar images, both visually and after calculating a HLR: AM uptake was considered significant when the HLR was over 1.8, a threshold value determined on the basis of the

Table 4 Clinical characteristics of patients with positive AM scintigraphy, in whom the treatment was modified from the time of evaluation

Patient	*1*	*2*	*3*	*4*	*5*	*6*
Disease	PAN	PAN	PAN	PAN	CS	PM
Organs involved (other than the heart)						
Lung					+	+
Kidney	+	+	+			
Skin			+			
Muscular			+			+
Peripheral neuropathy		+		+		
Polyarthritis			+			
GI tract	+	+	+			
Raynaud						
Treatments started from the time of evaluation (including AM scintigraphy)	CS 15 mg/kg CYC 0.6 g/m^2 PE ACEI 7.5 mg/d	CS 500 mg PE VB 15 mg/kg ACEI 25 mg/d CCB 50 mg/d	CS 1 mg/kg CYC 0.6 g/m^2 CCB 50 mg/d	CS 500 mg CYC 1 g	CS 1 mg/kg	CS 1 mg/kg CYC 0.6 g/m^2

PAN: periarteritis nodosa. CS: Churg-Strauss syndrome. PM: polymyositis. Scl: systemic sclerosis. GI tract: gastrointestinal tract. CS (dose per day): prednisone. CYC (dose per month): cyclophosphamide. MTX (dose per week): methotrexate. CSP: cyclosporine. VB: vidarabine. PE: plasmatic exchanges. ACEI: angiotensin converting enzyme inhibitor. CCB: calcium channel blocker.

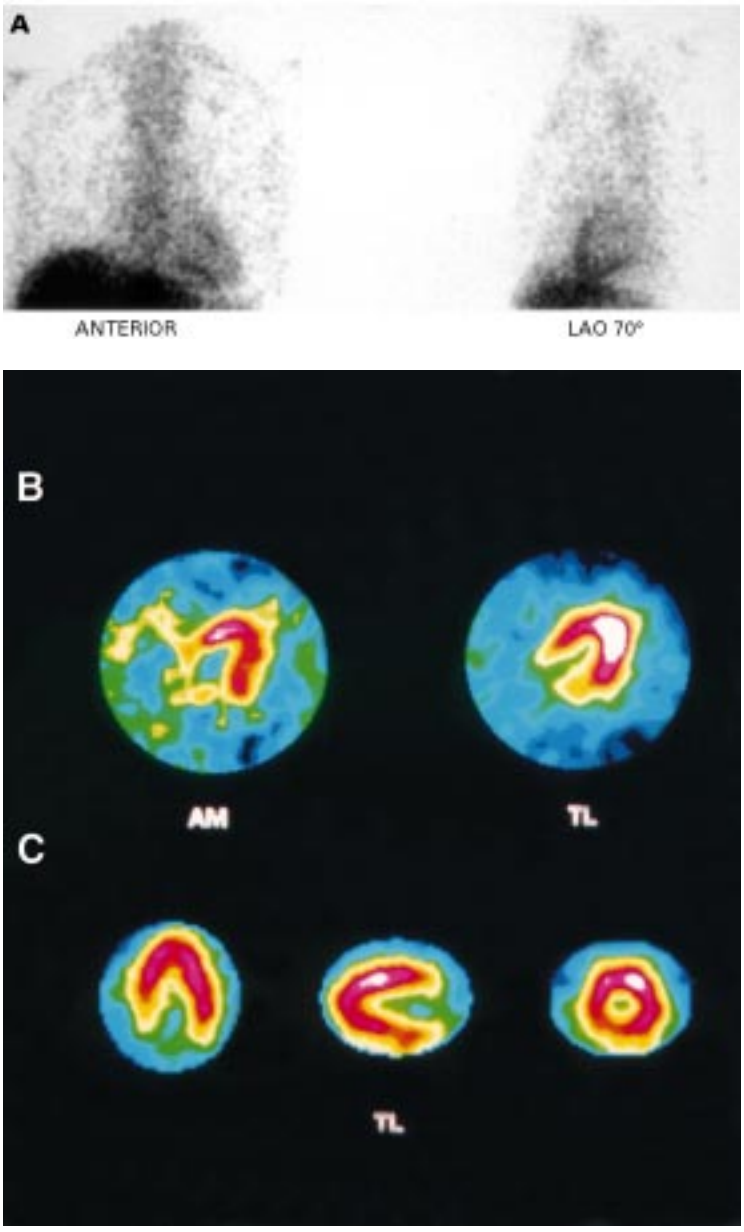

Figure 1 Initial scintigraphy of patient X (periarteritis nodosa), who presented with clinical LV failure (LV ejection fraction = 27%). Significant myocardial AM uptake is observed on the planar anterior view (A), HLR=2). Dual isotope SPECT (corresponding AM/Tl slices) shows diffuse AM uptake throughout the left ventricle (B), and normal Tl scan (C).

mean HLR + 2 SD in six healthy volunteers.[6] Mean difference in HLR values of the two observers was 5.12%. AM uptake was scored as diffuse or segmental on the basis of tomographic data.

The results of AM and Tl scintigraphy were compared with those of conventional investigations (clinical, electrocardiogram, echocardiography, and CPK assay), and then compared with follow up data.

2D ECHOCARDIOGRAPHY

Two dimensional echocardiography was performed with the patient supine, using a 2.5 MHz transducer fitted to a dedicated echocardiographic system (Hewlett-Packard Sonos 1500). Images were recorded on S-VHS videotape. Four standard views were used: parasternal long and short axis (at the level of the papillary muscles), and apical two and four chamber views. M-mode scans through the right parasternal axis of the left ventricle were obtained and recorded for quantification. All measurements were made as recommended by the American Society of Echocardiography. The following M-mode parameters were determined: end diastolic and end systolic LV diameters, septal and posterior wall thickness, and fractional shortening (FS). The measurements represented an average of 3–5 consecutive beats. All studies of a given patient were performed by a single experienced examiner unaware of the scintigraphic results.

FOLLOW UP

Clinical, electrocardiographic, and echocardiographic evaluations were repeated during follow up in every case. Scintigraphic follow up with delayed AM scans was also done three or six months, or both, after the first evaluation in six patients.

Results

SCINTIGRAPHIC RESULTS

Patients with cardiac signs of myocardial involvement (group 1)

Thirteen (43%) of the 30 patients in G1 had significant AM uptake (HLR = 2.06 (0.17)) on planar images (2 of 8 polymyositis, 3 of 4 polyarteritis nodosa, 2 of 4 lupus, 2 of 3 Churg-Strauss syndrome, 2 of 3 systemic sclerosis, 1of 3 dermatomyositis, 0 of 3 sarcoidosis,

Table 4 continued

7	*8*	*9*	*10*
PM	Scl	PR	Lupus
+			
			+
	+		+
+			
+		+	
	+		
CS 750 mg	Iloprost IV Penicillamine Amiodarone ACEI 5 mg/j	CS 0.5 mg/kg MTX 15 mg CSP 200 mg/d ACEI 5 mg/d	CS 60 mg ACEI 5 mg/d Furosemide 40 mg/d

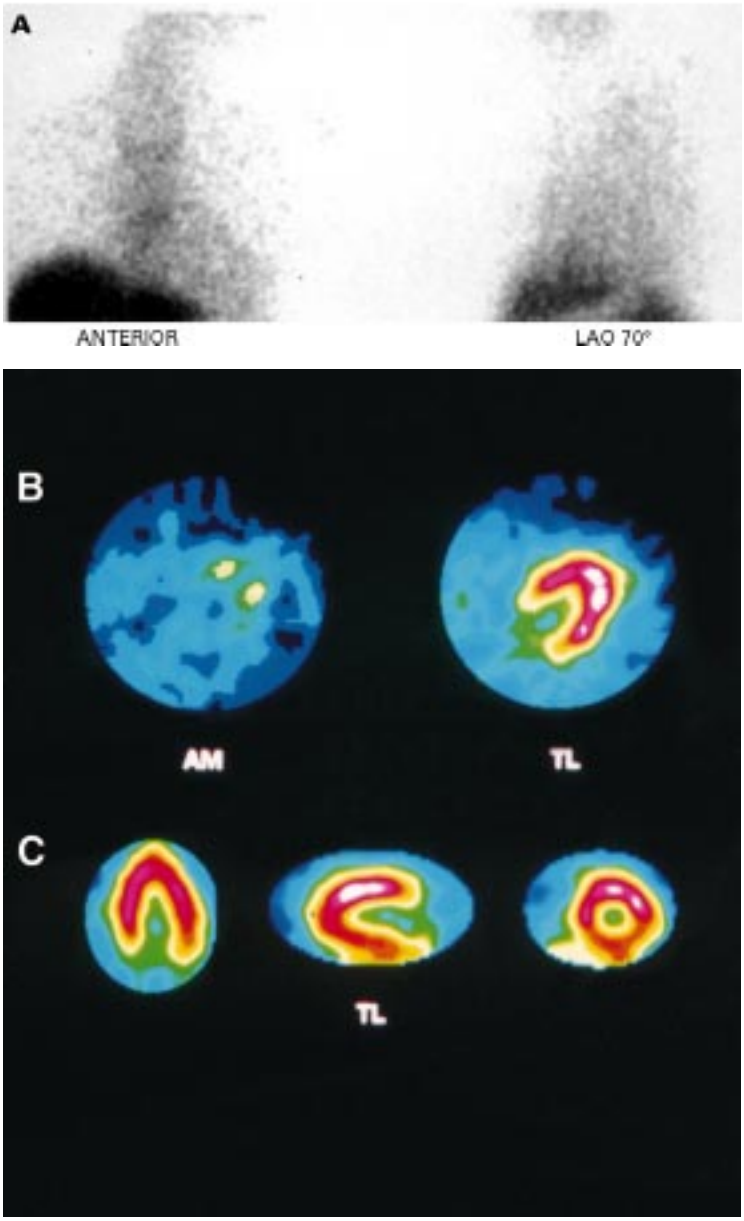

Figure 2 Delayed scintigraphy in patient X at six months. The cardiac manifestations have disappeared, and LV ejection fraction has increased to 41%. There is no more myocardial AM uptake on the planar anterior view (A), HLR=1.7), or on SPECT images (B): corresponding AM/Tl slices). Tl SPECT is normal (C).

1 of 1 rheumatoid arthritis, and 0 of 1 mixed connective tissue disease). Tomographic images showed that AM uptake was diffuse throughout the left ventricle in all 13 AM positive patients (right ventricle also in three), with a Tl defect in only four cases. In two of these patients AM uptake was much more intense in one particular region, with a matched Tl defect and matched regional hypokinesia on ultrasonography. All AM negative patients in G1 (n=17, HLR=1.45 (0.18)) had a homogeneous rest Tl scan.

Table 2 shows the percentages of patients with positive AM scans with respect to main cardiac abnormalities. All eight patients with acute or subacute clinical LV failure showed significant AM uptake. Among the 15 patients with echographic LV dysfunction, 11 had a positive AM scan. Conversely, two patients with positive AM scintigraphy had no clinical or echographic LV dysfunction, two were asymptomatic, and four had strictly normal ECG.

Table 3 reports the 2D echocardiographic and electrocardiographic findings according to the presence or absence of AM uptake. Mean (SD) LV fractional shortening (LVFS) was lower (23.2 (7.0)% versus 36.3 (5.7)%, p=0.000005), and mean LV diastolic diameter was higher (57.2 (5.4) mm versus 45.4 (5.0) mm, p=0.00003) in case of positive AM scintigraphy. Conversely, the frequency of electrocardiographic abnormalities was not different in patients with positive AM scans compared with patients with negative AM scans (77% versus 76%).

Patients with no signs of myocardial involvement (group 2)

All the patients in G2 had negative AM scintigraphy (HLR=1.48 (0.10)) and a normal Tl scan. There was no statistical difference in mean (2SD) HLR values between the AM negative patients in G1, G2 and the normal control group (HLR=1.50 (0.15)). Mean LVFS was higher in G2 than in AM positive G1 patients (38.2 (3.6)% versus 23.2 (7.0)%, p=0.000004), and was not different from that in G1 patients with negative AM scintigraphy (38.2 (3.6)% versus 36.3 (5.7)%, NS).

FOLLOW UP

Follow up was obtained in 36 of 40 patients, and lasted from 3 to 78 months (mean (SD): 17 (19) months).

Patients with myocardial AM uptake

Twelve of the 13 AM positive patients were followed up.

In two of these 12 patients, diffuse infectious myocarditis was initially diagnosed (cytomegalovirus and *Borrelia burgdorferi*), and antimicrobial chemotherapy was started. One patient died after acute LV failure and cardiac arrest, while the other remained stable with severe LV dysfunction despite antibiotic treatment.

In the remaining 10 patients, specific treatment was increased (immunosuppressive drugs in nine, intravenous vasodilators in one with systemic sclerosis, see table 4) and cardiac sta-

tus improved in nine cases. Six patients showed improved LV function (LVFS increased from 22.5% to 33.0%, p=0.02). In two patients initial electrocardiographic abnormalities disappeared after three months. In one, the initial pericarditis resolved while the left bundle branch block persisted (LV function was always normal). Six of these nine patients underwent control AM scintigraphy three months later: all but one were normalised (figs 1 and 2). LVFS fell in the 10th patient despite intensified corticosteroid treatment: delayed AM scans remained positive in this patient.

Patients without significant myocardial AM uptake

Twenty four of 27 patients with negative AM scintigraphy were followed up.

In 20 cases the immunosuppressive treatment was unchanged and no cardiac treatment was started. In the other four cases the treatment was intensified because of progressive pulmonary, renal or muscle involvement.

Cardiac status was considered stable in 23 of 24 patients during follow up, even in three patients who died of severe pulmonary or renal involvement, or both. No new cardiac events occurred, and the electrocardiograms remained stable (strictly normal in G2 patients). Four of these patients had mild chronic LV dysfunction, which was noted as specific in two, secondary to pulmonary involvement in one, and secondary to severe hypertensive cardiomyopathy in another patient treated with cyclosporine for polymyositis. Left ventricular fractional shortening in these patients was not changed during follow up, suggesting sequellary myocardial injury (31.3 (4.6)% to 32.3 (5.7)%, NS). LVFS remained normal in the other 19 patients.

One G1 patient with dermatopolymyositis developed mild LV dysfunction after 36 months, during a subacute exacerbation of skin and muscle involvement.

Discussion

The prognosis of patients with systemic diseases and primary cardiac involvement is poor. Cardiac involvement is the third cause of death in lupus and polymyositis, and is responsible for 25% of deaths in systemic sclerosis.[7–12] Early recognition of active myocardial disease, before the onset of overt heart failure, may improve treatment and prognosis.[1] However, a large proportion of myocardial disease is not detected. In systemic sclerosis, for example, the clinical incidence is only 7% to 16%, while necropsy studies show microscopic changes in up to 89% of cases.[13–15] Clinical, electrocardiographic, and echocardiographic signs are nonspecific, especially in the presence of pulmonary or renal injury. Perfusion scintigraphy has potential value,[16–18] but may miss diffuse equilibrated myocardial injury.[19] Moreover, none of these methods discriminate between active and sequellary myocardial disease. Finally, the diagnosis of specific myocardial involvement is based on histological studies after endomyocardial biopsy. However, the use of endomyocardial biopsy has rarely been reported in this indication, as it is an invasive method with poor sensitivity; in addition, it is not free of complications and cannot be repeated during follow up.[2–4 20]

The diagnostic value of AM, which binds specifically to damaged myocytes, has been reported in several types of myocardial diseases, including myocardial infarction, drugs cardiotoxicity, idiopathic dilated cardiomyopathy, alcoholic cardiomyopathy, cardiac rejection after heart transplantation, and myocarditis of infectious or other origins.[21–27] This study demonstrates that AM scintigraphy coupled with rest Tl imaging may also be of interest in assessing active myocardial damage related to systemic diseases. Significant myocardial AM uptake and a normal Tl SPECT is suggestive of ongoing patchy myocytes necrosis, which is a marker of active process of myocardial damage, whatever the underlying disease. Rest Tl abnormalities may be explained by chronic hypoperfusion (as in microvascularitis) or by fibrosis caused by myocyte necrosis.

AM scintigraphy is a sensitive method (83% to 100%,) for detecting diffuse myocyte necrosis in myocarditis.[26 27] Only isolated cases of AMA imaging have been reported in immune myocardial diseases.[28–30] In our study the sensitivity of AM scintigraphy for active myocardial damage could not be determined in the absence of a diagnostic gold standard. However, it is worth noting that all the patients with clearly active myocardial disease, who showed modification in cardiac status during follow up, had a positive AM scan. Moreover, AM scintigraphy detected myocardial damage in two asymptomatic patients, in four others with normal ECG, and in nine with strictly normal Tl scans. In addition, two patients with positive AM scintigraphy had a normal LV on echocardiography; the normalisation of AM scintigraphy three months after intensification of specific treatment, together with the disappearance of atrioventricular block in one and pericarditis in the other, indirectly confirmed recent resolutive LV injury. Finally, the fact that no further cardiac events occurred in the patients without myocardial AM uptake despite treatment not being increased in most of them, suggests a good negative predictive value.

Poor specificity has been reported in several studies in the diagnosis of myocarditis (31% to 58%).[26 27] However, these values are probably underestimations because of the low sensitivity of endomyocardial biopsy used as the gold standard. In a recent report Mason *et al* found that fewer than 10% of biopsies were positive in patients with a typical history of acute myocarditis.[24] In this study, the normality of the HLR in G1 patients free of new cardiac events during follow up, with results identical to those in patients not suspected for cardiac involvement and in normal volunteers, indirectly indicate good specificity. It is worth noting that a negative AM scan does not exclude sequellary myocardial involvement, as observed in two patients with chronic stable LV dysfunction not explained by causes other than the systemic disease. The improvement of cardiac status after intensification of specific treatment in 9 of

10 AM positive patients, and the normalisation of AM scintigraphy in 6 of 7 of them are other arguments for a good specificity.

Active myocardial damage revealed by AM uptake can have several causes. Dual isotope tomographic acquisition was useful in eliminating segmental myocardial infarction resulting from the occlusion of an epicardial coronary artery, as AM uptake was always diffuse throughout the left ventricle, and sometimes also by the right ventricle. The main limitation of this method is its inability to determine the cause of diffuse active myocardial injury, especially to discriminate between primary cardiac involvement and infectious myocarditis in patients receiving immunosuppressive therapy. This diagnostic dilemma was encountered twice in our study. Of note, AM antibody uptake by the skeletal muscles has been reported in inflammatory muscles disease. But in our experience, images of the thighs muscles in 14 patients with polymyositis and high CPK concentrations were always negative.

Discordant patterns of LV function and AM uptake can be observed, with a positive AM scan and normal LV function, or a negative AM scan despite LV dysfunction. Ballester explained these discrepancies by the fact that LV function results in the combination of different factors: the degree of recent myocyte necrosis (detected by AM imaging), the amount of fibrotic tissue (myocardial mass loss not detected by AM imaging), and the proportion of purely functionally impaired myocardium.[25] In systemic diseases, myocyte death may be of ischaemic origin (injury of the microvessels), or related to cytotoxic immune pathways. Reversible functional impairment of the myocardium, without myocyte necrosis, may also be induced by ischaemia or by interleukin 1 and tumour necrosis factor release by macrophages.[31] Changes in LV function during treatment may thus depend on several factors, including the treatment itself, the disease, and its duration. As a result, current disease activity may be accurately assessed on the basis of both LV function changes and AM imaging, which reveals active necrosis only.

Theoretically, the repeated use of AM antibodies may induce anti-murine immune reaction. However in previous reports, human anti-murine antibodies were not detectable in patients with repeated injections, and no adverse reaction was observed.[23–26]

Each of the disease subgroups of our study population included only few patients. So larger series may be required for further confirmation of our results. In particular, the sensitivity of AM scintigraphy may differ from one disease to another, depending on the amount of necrosed myocytes induced by active process of myocardial damage.

In conclusion, [111]Indium antimyosin antibody scintigraphy permits detection of active myocardial damage related to systemic diseases, with increased specificity compared with conventional methods, and increased sensitivity in some cases. Further studies are needed to assess the potential value of AM scintigraphy as a therapeutic guide.

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