Time Course of Myocardial Infarction Evaluated by Indium-111-Antimyosin Monoclonal Antibody Scintigraphy: Clinical Implications and Prognostic Value

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To investigate the clinical implications of ^{111}In-antimyosin antibody scintigraphy in the chronic stage of myocardial infarction, 34 studies were performed in 26 patients with 36 infarcts of various infarct ages. The infarcts were divided into three groups according to time from onset of chest pain to scintigraphy. Positive antimyosin images were obtained in 93% of Group I patients (3 days to 1 mo), 71% of Group II patients (1.5 mo to 1 yr) and none were obtained from Group III patients (1.5–6 yr). A negative correlation was observed between antimyosin uptake and the time after myocardial infarction. In Group II, patients with coronary artery patency and patients showing redistribution on exercise ^{201}Tl scintigraphy were more likely to have positive antimyosin images compared to patients without these features. Recurrent angina may also relate to chronic antimyosin uptake. Indium-111-antimyosin antibody scintigraphy may be a useful method in assessing the course of myocardial infarction and for the patient follow-up.

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Myocardial scintigraphy using an ^{111}In-labeled antimyosin monoclonal antibody developed by Khaw et al. (*1–2*) has been reported to be useful for the noninvasive detection of myocardial necrosis (*3–6*). This method was initially used to evaluate myocardial damage in patients with acute myocardial infarction (MI), but it has subsequently been found also to detect damage in the subacute and chronic stages of MI (*7–10*) when myocardial necrosis should be replaced by fibrous tissue. This feature may be useful in the diagnosis of suspected MI up to several months after the onset, when early electrocardiographic (ECG) changes and serum cardiac enzyme elevation have resolved (*7*), although it may also reduce the specificity of ^{111}In-antimyosin scintigraphy for imaging acute myocardial necrosis (*11*). How long this type of scintigraphy can detect myocardial necrosis and what the clinical implications of persistent antimyosin uptake are remains unclear (*12*). To clarify these issues, we performed 34 ^{111}In-antimyosin scintigraphic studies at various times after MI (3 days to 6 yr) and investigated the clinical factors which may affect ^{111}In-antimyosin uptake in the chronic stages of infarction. A follow-up ^{111}In-antimyosin study was done in eight patients to compare the changes over time in the same patients.

MATERIALS AND METHODS

Patient Population

Thirty-four ^{111}In-antimyosin studies were performed in 24 patients with single-vessel-related MI and in 2 patients with two-vessel-related MI (23 males and 3 females, aged 47 to 83 yr, mean age 64.4 yr). The patients had 36 infarcts of varying ages that were divided into three groups according to the time from onset of chest pain to the injection of ^{111}In-antimyosin antibody (onset - injection time). Group I included patients whose onset - injection time was less than 1 mo, Group II patients had times ranging from 1 mo to 1 yr, and Group III patients had times from 1 yr to 6 yr (Table 1). A follow-up study was done in eight patients at 3 mo to 1 yr after the first scan (mean: 9.6 ± 2.2 mo). Acute MI was diagnosed on the basis of precordial chest pain typical of myocardial ischemia lasting for at least 30 min, ST-segment elevation of at least 0.1 mV with subsequent evolution of an infarct pattern on the ECG and significant elevation of the serum creatine phosphokinase (CK) level. Selective coronary angiography was performed in all patients and the infarct-related findings are listed in Table 1. Revascularization by percutaneous transluminal coronary angioplasty (PTCA) was performed on the day of admission in 17/36 acute MIs. Left ventriculography (LVG) was performed at discharge in all but three patients. Exercise ^{201}Tl scintigraphy was performed using SPECT in 29/36 infarcts during the first admission, as reported previously (*13*). A fixed defect was defined as the perfusion defect in the initial image persisting in the delayed image and redistribution was defined as the hypoperfused area in the first image showing a decrease in the delayed image. Further ischemic events concerning the infarct-

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TABLE 1

Results of ^{111}In-Antimyosin Antibody Scintigraphy and Clinical Data of 36 Myocardial Infarcts

Group I

No.	Age	Sex	ECG location	onset - imaging	Antimyosin data +/-	AM-score	HLR	peak CK	PTCA	CAG (Infarct-related)	ECG Q-wave	LVG EF (%)	TL-201 finding	further ischemic event before imaging	after imaging
I-1	52	M	Inferior	3 days	+	3+	2.34	1609	—	RCA : 99 %	Q	69	FD	—	—
I-2	60	M	anterior	3 days	+	3+	—	9170	+	LAD : 100 % -> 50 %	Q	63	Red	—	angina
I-3	74	M	Inferior	5 days	+	2+	—	1886	—	RCA : 100 %	Q	30	—	—	angina
I-4	61	M	Inferior	6 days	+	3+	2.29	2400	—	RCA : 100 %	Q	35	FD	—	—
I-5	69	M	anterior	6 days	+	2+	—	1117	+	LAD : 90 % -> 25 %	non-Q	72	Red	—	—
I-6	83	M	anterior	8 days	+	2+	—	511	+	LAD : 99 % -> 25 %	Q	58	Red	—	—
I-7	64	M	anterior	8 days	+	3+	—	12456	—	LAD : 99 %	Q	—	—	—	in hospital death
I-8	63	M	anterior	10 days	+	2+	1.86	2451	—	LAD : 90 %	Q	33 (Aneu)	FD	—	—
I-9	63	M	anterior	11 days	+	3+	2.68	4160	—	RCA : 100 %	Q	57	FD	—	—
I-10	72	M	Inferior	12 days	+	2+	1.57	1160	+	Cx : 100% -> 25 %	non-Q	34	Red	—	angina
I-11	66	M	lateral	16 days	+	3+	1.85	—	—	Cx : 99 % (+C)	non-Q	50	Red	—	—
I-12	59	M	anterior	24 days	+	3+	2.68	4756	—	LAD: 90 %	Q	45(Aneu)	FD	—	VT, restenosis
I-13	55	M	Inferior	1 mo	+	3+	2.85	1949	—	RCA: 100 % (+C)	Q	32	—	—	—
I-14	60	M	anterior	1 mo	—	1+	1.43	—	—	LAD : 99 % (+C)	Q	56	Red	—	angina
mean	64 ± 8			12 ± 9 days				3635 ± 3632				49 ± 15			

Group II

No.	Age	Sex	ECG location	onset - imaging	Antimyosin data +/-	AM-score	HLR	peak CK	PTCA	CAG (Infarct-related)	ECG Q-wave	LVG EF (%)	TL-201 finding	further ischemic event before imaging	after imaging
II-1	72	M	Inferior	1.5 mo	+	2+	—	3975	+	RCA : 100 % -> 25 %	Q	43(Aneu)	Red	—	aneurysmectomy
II-2	64	M	Inferior	2 mo	+	2+	1.63	869	—	RCA : 99 % (+C)	Q	72	Red	—	—
II-3	51	M	anterior	2 mo	+	2+	1.93	—	—	LAD : 99 %	Q	48	Red	—	restenosis
II-4 *	59	M	anterior	3 mo	+	2+	1.98	4756	—	LAD : 90 %	Q	45(Aneu)	FD	—	—
II-5 **	68	M	Inferior	3.5 mo	+	2+	—	4845	+	RCA : 90 % -> 50 %	Q	36	—	—	CABG
II-6 **	51	M	anterior	4 mo	+	2+	1.67	—	+	LAD : 100 % -> 50 %	non-Q	66	Red	—	—
II-7 **	51	M	lateral	8 mo	—	1+	1.34	—	—	Cx : 100 %	Q	—	—	—	—
II-8	59	M	anterior	9 mo	+	2+	1.63	3402	+	LAD : 90 % -> 25 %	Q	46	Red	—	restenosis
II-9 *	64	M	anterior	10 mo	+	2+	1.49	2451	—	LAD : 90 %	Q	33(Aneu)	FD	angina	—
II-10 *	64	M	Inferior	11 mo	—	1+	1.41	4160	—	RCA : 100 %	Q	57	FD	—	—
II-11 *	57	M	Inferior	1 yr	+	2+	1.91	1949	—	RCA : 100 % (+C)	Q	32	Red	angina	—
II-12 *	53	M	anterior	1 yr	—	1+	1.44	—	—	LAD : 99 %	Q	48	FD	angina	—
II-13 *	53	M	Inferior	1 yr	—	0	1.23	1609	—	RCA : 99 %	Q	69	FD	—	—
II-14 *	73	M	Inferior	1 yr	+	2+	1.54	1160	+	Cx : 100 % -> 25 %	non-Q	34	Red	angina	CABG
mean	60 ± 8			7.3 ± 4.4 mo				2918 ± 1496				48 ± 14			

TABLE 1 *continued*

Group III

No.	Age	Sex	ECG location	onset - imaging	Antimyosin data +/-	AM-score	HLR	peak CK	PTCA	CAG (Infarct-related)	ECG Q-wave	LVG EF (%)	TL-201 finding	further ischemic event before imaging	after imaging
III-1	62	M	Inferior	1.5 yr	—	0	1.30	2139	+	Cx : 100 % -> 50 %	Q	61	Red	—	—
III-2 *	60	M	anterior	1.5 yr	—	1+	1.38	3402	+	LAD : 90 % -> 25 %	Q	63	FD	restenosis	—
III-3	71	F	anterior	1.5 yr	—	1+	—	—	+	LAD : 100 % -> 25 %	non-Q	28	FD	angina	—
III-4	74	M	anterior	2 yr	—	0	1.24	—	—	LAD : 100 %	Q	57	—	angina	—
III-5	62	M	Inferior	2 yr	—	0	—	—	—	RCA : 99 %	Q	38	FD	—	—
III-6	73	F	Inferior	2.5 yr	—	1+	—	—	+	RCA : 100 % -> 25 %	non-Q	39	—	—	—
III-7 **	68	M	anterior	5 yr	—	0	—	—	+	LAD : 99 % -> 25 %	Q	36	—	—	CABG
III-8	81	F	anterior	6 yr	—	0	—	—	—	RCA : 90 %	Q	—	—	—	—
mean	69 ± 7			2.8 ± 1.8 yr								46 ± 14			

* follow-up study ** recurrent AMI

LAD ; left anterior descending artery, RCA ; right coronary artery, Cx ; circumflex artery

Red : redistribution (+) FD : fixed defect

(+c) : with collateral flow

Aneu : aneurysmal VT : ventricular tachycardia

CABG : coronary - artery bypass grafting

related vessel are also listed in Table 1 and are divided into the events occurring before and after ^{111}In-antimyosin scintigraphy. All patients gave written informed consent to the study, which was approved by the hospital human investigation ethics committee.

Radiopharmaceuticals

To test for hypersensitivity, all patients received an intradermal skin test with 0.05 mg/0.1 ml of diethylenetriamine pentaacetic acid (DTPA)-antimyosin monoclonal antibody (Fab fraction). If there was no weal or flare reaction, 0.5 mg/2 ml of antimyosin antibody labeled with 74 MBq (2 mCi) of ^{111}In (Daiichi Radioisotope Laboratories, Ltd, Tokyo, Japan) was slowly injected intravenously over 30–60 sec.

Protocol

Forty-eight hours after intravenous injection of the ^{111}In-antimyosin antibody, planar images were obtained in the anterior, 45° left anterior oblique and left lateral views. Images were obtained for 7 min in each view using a medium-energy, general-purpose collimator to collect 300–500 kilocounts from both photopeaks of ^{111}In (174 and 247 keV). SPECT was performed subsequently after planar imaging. A series of 64 projection images were collected ever 360° at 5.6° increments for 30 sec each using a 64 × 64 matrix and then were stored for image analysis. A series of transaxial slices at 6-mm intervals were reconstructed by a filtered backprojection method. A series of vertical long-axis, horizontal long-axis and short-axis sections were also obtained.

Image Analysis

The planar and SPECT antimyosin images were interpreted directly from the computer video display by two observers who had no knowledge of the clinical data. Any differences were resolved by consensus, and these results were used as the final interpretation.

Antimyosin Score. The intensity of myocardial antimyosin uptake was graded from zero to 3+; for planar images: zero, no definite uptake in the heart; 1+, diffuse faint uptake by the myocardium; 2+, discrete myocardial uptake that was less than the hepatic uptake; and 3+, discrete myocardial uptake with an intensity similar to or greater than the hepatic uptake. Uptake grades 2+ and 3+ were considered to be positive, while grades zero and 1+ were considered to be negative.

Heart-to-Lung Ratio (HLR). Myocardial antimyosin uptake was quantitatively evaluated in 24 infarcts. The HLR was calculated from the computer display system by dividing the average counts per pixel in the myocardium by the average counts of the left lung in the left anterior oblique image according to the method of van Vlies (*4*).

Statistical Analysis

All data are expressed as the mean ± one standard deviation. Analysis of variance was used to assess the differences between groups and between the first and second studies (*14*). Chi-squared analysis or Fisher's exact test was used to determine the differences between proportions, A p value of <0.05 was considered significant.

RESULTS

There were no significant differences among the three groups regarding ECG localization of MI, the infarct-related vessels, the ejection fraction at discharge, the performance of PTCA or the extent of collateral flow, and the presence of Q- or non-Q-wave infarction (Table 1).

Indium-111-antimyosin uptake was positive in 13/14 studies (93%) in Group I, 10/14 studies (71%) in Group II, and 0/8 studies (0%) in Group III (Table 2). The antimyosin uptake evaluated visually using the antimyosin score correlated well with that evaluated quantitatively using the HLR. The mean antimyosin score and the mean HLR for each group are shown in Table 2. Two patients demonstrated intense antimyosin uptake in the anterior wall up to 2–3 mo after MI (Patient II-3; HLR 1.93, Patient II-4; HLR 1.98). Patients studied after 4 mo demonstrated lower antimyosin scores than those studies before this time. Two patients with acute MI and a prior infarct showed positive images only at the site of the recent MI. A negative correlation was observed between the HLR and the time after MI ($r = -0.67$, $p < 0.01$) (Fig. 1).

A clinical evaluation was done for Group 2 patients to identify factors related to scintigraphic positivity in the chronic stage of MI. All seven patients with patent coronary arteries (residual stenosis <75% or good collateral flow) showed positive antimyosin uptake in comparison with three of seven without patency ($p < 0.05$). Furthermore, all seven patients in whom exercise ^{201}Tl scintigraphy demonstrated redistribution at the first admission showed positive antimyosin uptake when compared with two of five patients in whom a persistent defect was demonstrated ($p < 0.01$). Patients who showed positive images 10 mo or 1 yr after onset had a history of recurrent

TABLE 2
Results of ^{111}In-Antimyosin Antibody Scintigraphy

Interval from the onset to imaging	Positive	Negative	Antimyosin score	HLR
Group I (3 days–1 mo)	13 (93%)	1 (7%)	2.5 ± 0.7	2.17 ± 0.52
Group II (1 mo–1 yr)	10 (71%)	4 (29%)	1.6 ± 0.6*	1.60 ± 0.24‡
Group III (1 yr–6 yr)	0 (0%)	8 (100%)	0.4 ± 0.5†	1.31 ± 0.07†

† $p < 0.001$ vs. Group I.
* $p < 0.01$ vs. Group I.
‡ $p < 0.05$ vs. Group 1.

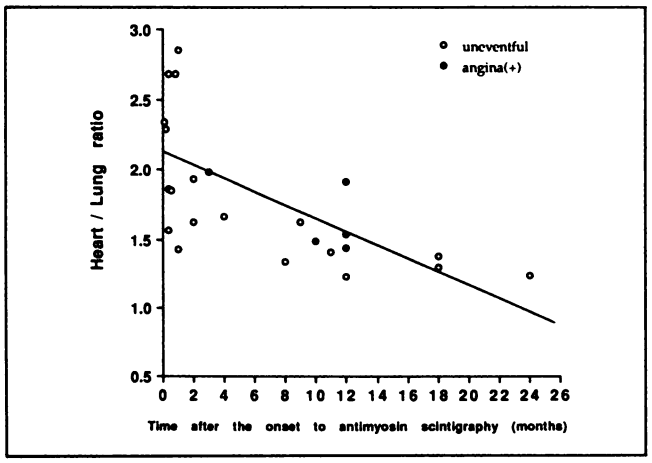

FIGURE 1. The HLR of patients at various times after the onset of acute MI. The HLR gradually decreased with time (Y = 2.08–0.045X, $p < 0.05$). Open circles = patients with an uneventful course and closed circles = patients with angina after acute myocardial infarction.

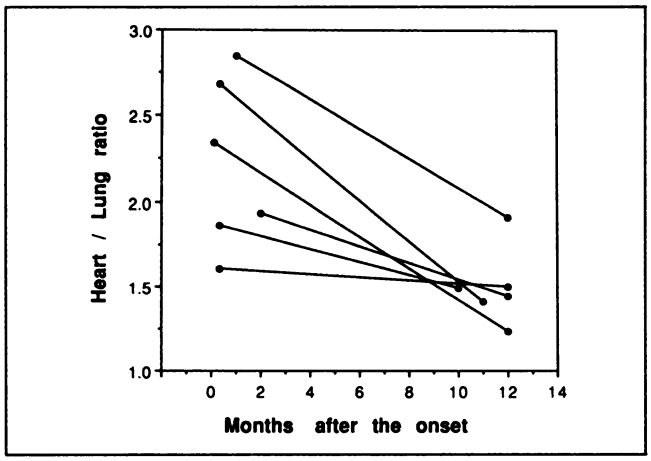

FIGURE 2. Plots of HLR values for six patients who underwent follow-up ^{111}In-antimyosin scintigraphy. The mean HLR decreased in the second study when compared with that in the first study.

angina but no evidence of ECG changes or CK elevation (Fig. 1).

A follow-up study was performed in eight patients in whom acute and chronic images were obtained for six (mean follow-up period; 11 ± 1.0 mo). For these six patients, the mean HLR decreased significantly from 2.21 ± 0.70 to 1.50 ± 0.47 ($p < 0.01$) (Fig. 2). Of the four patients with a positive image in the second study, three had a history of recurrent chest pain suggesting restenosis (Patients II-9, II-11 and II-14). The ejection fraction determined by LVG at the time of discharge after the first admission was significantly lower in patients who were positive in the second imaging study than in those who were negative (39% ± 7% versus 55% ± 10%, $p < 0.01$). The localized antimyosin uptake noted in the acute stage disappeared in the second study in one patient (Fig. 3), but persisted in another patient (Fig. 4). The clinical course was uneventful in the former, while the latter had suffered from recurrent angina. The extent of antimyosin uptake demonstrated on the SPECT images of the patient shown in Figure 4 was similar in both the first and second studies (Fig. 5). One patient who showed focal but definite myocardial uptake at 9 mo after MI (Patient II-4) demonstrated the loss of radioactivity at the center of the lesion in the follow-up study performed 9 mo later (Patient III-2) (Fig. 6).

DISCUSSION

The aging process of infarcts has been histologically investigated (*15–18*). Myocardial cell necrosis is gradually replaced by fibrous tissue after acute and chronic inflammatory responses have occurred. Much of the necrotic muscle is removed between the second and fourth weeks after MI, although the rate of healing is reported to vary widely and necrosis may persist for several months after the infarct (*15,18*). This study showed that the intensity of antimyosin uptake decreased with time. The HLR value indicating the border between a positive and a negative scintigram is around 1.50, as shown by evaluating the regression line in Figure 1, a result that is compatible with the reports of other authors (*6,19*). Surprisingly, intense ^{111}In-antimyosin uptake was demonstrated 2–3 mo after

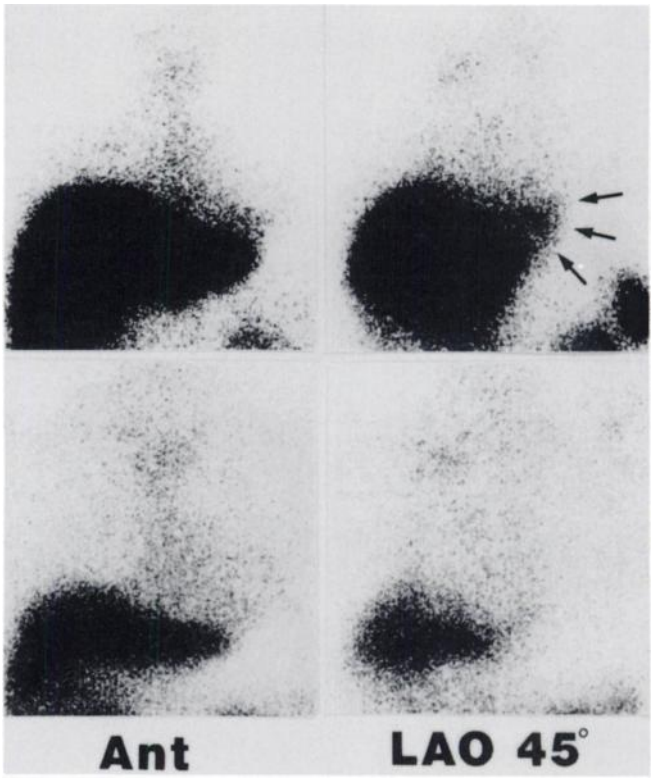

FIGURE 3. Planar ^{111}In-antimyosin scintigraphic images obtained at 3 days after the onset of MI (upper images) and 1 yr later (lower images). Definite inferior myocardial uptake is seen right above the liver in the first study (arrows, HLR, 2.34), while no uptake can be seen in the second (HLR, 1.23).

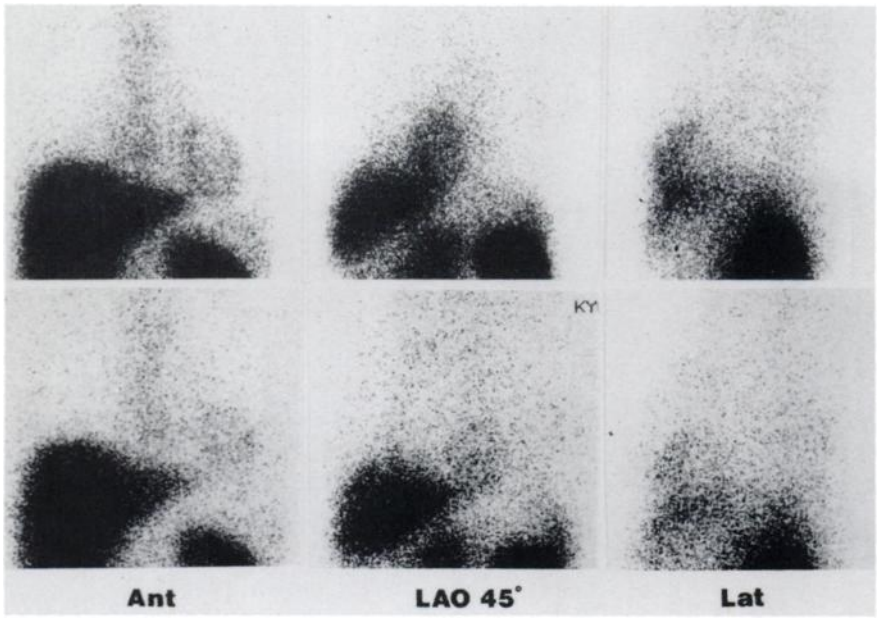

FIGURE 4. Planar ^{111}In-antimyosin scintigraphic images obtained at 10 days after myocardial infarction (upper images) and 10 mo later (lower images). Definite myocardial uptake is seen in the anterior wall in the first study (HLR, 1.86), and persistent but decreased uptake is seen in the second (HLR, 1.49). Ant = anterior view; LAO 45 = left anterior oblique 45° view and Lat = lateral view.

MI in some of our patients. These patients did not suffer from recurrent angina or CK elevation and lacked coronary artery patency. These results suggest that ^{111}In-antimyosin scintigraphy may be useful to distinguish early and alter infarcts only when the interval between them is more than 2–3 mo. The mechanism of antimyosin uptake is believed to be related to loss of cell membrane integrity allowing access to the myosin heavy chain inside necrotic myocytes (*20,21*). However, another mechanism is required to explain the persistent positive antimyosin uptake that we noted, such as chronic inflammatory response that occurs after acute MI. In large infarcts, inflammatory cells initially cannot access the infarct center, and dead myocytes can persist for a number of weeks until new capillaries grow into the region (*18*). In humans, infarcts are not completely transmural (*22*) and the histological changes after MI have become more complicated since the introduction of reperfusion therapy (*23,24*). Thus, areas of

FIGURE 5. Single-photon emission computed tomograms in the short-axis view from a patient with anterior MI (Fig. 4) obtained during the first (upper images) and second (lower images) ^{111}In-antimyosin scintigraphic studies. The extent of antimyosin uptake is similar in the two images.

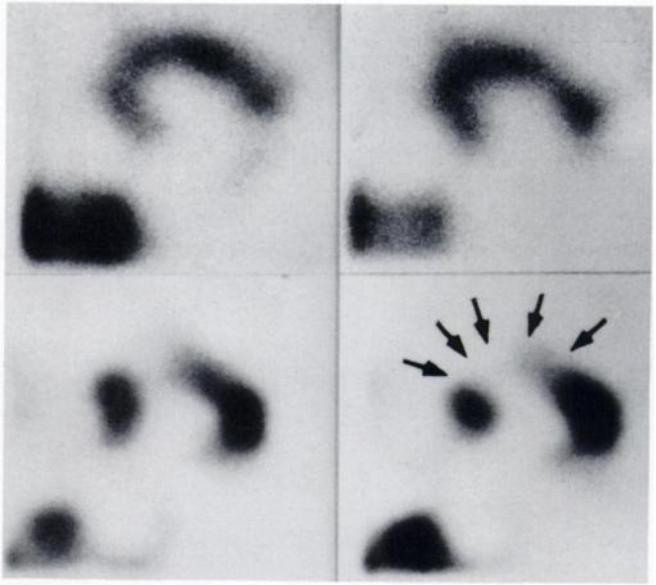

FIGURE 6. Single-photon emission computed tomograms in the short-axis view from a patient with anterior MI obtained during the first (Patient II-8, upper images) and second (Patient III-2, lower images) ^{111}In-antimyosin scintigraphic studies. Note the loss of radioactivity at the center of the lesion that had been positive in the initial study (arrows).

variable cellular injury consisting of necrotic and surviving myocardium may be present. We have previously reported that injected antimyosin antibody could be detected immunohistochemically even 3 mo after coronary artery ligation in rabbits with experimental MI (*25*). Positive antimyosin staining was observed in the surviving myocytes around the scar tissue and not in the scar itself. The mechanism of the chronic antimyosin uptake noted in the current study may be related to such myocytes, to ongoing necrosis due to the inflammatory response or to both of these factors. Thus, further studies on this subject are required.

The clinical implications of chronic positive antimyosin uptake are one of the current issues in relation to ^{111}In-antimyosin scintigraphy (*12*). In our follow-up study, patients with recurrent chest pain or poor cardiac function were more likely to demonstrate chronic positive antimyosin uptake than patients with an uneventful course. Such patients tend to have poor prognoses (*26*). Therefore, it may be possible that chronic antimyosin uptake reflects residual ischemia, although definite evidence of myocardial necrosis-like CK elevation or ECG changes was not observed in the interval between the first and second ^{111}In-antimyosin studies. Van Vlies et al. have reported on the predictive value of ^{111}In-antimyosin scintigraphy in MI (*4*). They stated that intense early antimyosin uptake was related to extensive regional asynergy at the time of discharge from the coronary care unit. Our observations may suggest that ^{111}In-antimyosin scintigraphy has prognostic value in the chronic stage of MI and that follow-up antimyosin studies may be of value to evaluate chronic antimyosin uptake. When persistent antimyosin uptake is shown several months to 1 yr after MI, residual ischemia may be present and further clinical studies including coronary angiography may be required. A persistent positive image after acute MI has also been reported in ^{99m}Tc-pyrophosphate scintigraphy as a marker of a poor prognosis (*27,28*). In addition, follow-up studies with ^{111}In-antimyosin scintigraphy have been reported to have a prognostic value in patients with myocarditis and heart transplantation. Dec et al. (*29*) reported that such studies were useful for distinguishing acute myocarditis from dilated cardiomyopathy. Ballester-Rodes et al. (*30*) reported that repeated ^{111}In-antimyosin imaging was useful in defining the outcome and in determining management noninvasively after heart transplantation, because rejection-related complications could be suspected if antimyosin uptake persisted or increased.

Following the salvage of myocardial viability, residual myocardial ischemia and further ischemic events are not uncommon. Johnson et al. found that dual ^{111}In-antimyosin and ^{201}Tl SPECT were useful for separating patients with an additional ischemic region at risk from those likely to have a benign in-hospital course (*31*). They reported that the former group were likely to show overlap on ^{111}In-antimyosin and ^{201}Tl studies. A mixture of salvaged myocytes and necrotic myocytes may be present in the positive regions in such patients. We found that Group 2 patients with redistribution on exercise ^{201}Tl scintigraphy and coronary artery patency were more likely to have chronic positive antimyosin uptake when compared to those with a persistent defect or without coronary patency. These findings may also suggest that residual myocardial viability and persistent ischemia may lead to chronic antimyosin uptake.

CONCLUSION

Positive ^{111}In-antimyosin images could be obtained until 1 yr after the onset of MI, although antimyosin uptake gradually decreased with time. A negative correlation was observed between antimyosin uptake and the time after MI. In patients with chronic MI (1 mo to 1 yr after onset), coronary artery patency and residual myocardial viability detected by exercise ^{201}Tl scintigraphy at the first admission were related to positive antimyosin images. Recurrent angina may also relate to chronic antimyosin uptake from several months to 1 yr after MI. Follow-up ^{111}In-antimyosin scintigraphy may be useful in evaluating the course of MI, and persistent uptake may indicate a worse prognosis.

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