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Myocardial uptake of antimyosin antibody compared with serum myosin light chain I levels in patients with myocardial infarction

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Myocardial accumulation of In-111-antimyosin (InAM) was evaluated in comparison with circulating serum myosin light chain I (LCI) level at the time of InAM injection. Seventeen consecutive patients were studied at various stages ranging from 6 days to 34 days after myocardial infarction (MI). The infarct area was positive for InAM uptake in all patients (100%), and significant myocardial uptake was observed in 14 patients (82.4%). The intensity of InAM uptake correlated with the infarct location shown by ECG and CAG. In contrast, 12 patients (70.6%) had normal or undetectable serum myosin LCI levels, with 5 being normal (0.42–2.5 ng/m*l*) and 7 undetectable (0.42 ng/m*l* or less). Only 5 patients (29.4%) had elevated serum myosin LCI levels at the time of InAM injection, and this elevation was slight, ranging from 3.4 to 4.5 ng/m*l* (mean: 3.75 ng/m*l*). Among patients with undetectable, normal, and elevated serum myosin LCI levels, there was no significant correlation between InAM uptake and the serum myosin LCI level. Thus, even after the serum myosin LCI level has decreased to normal, InAM can still bind to cardiac myosin in patients with MI, presumably until there is complete recovery from the hibernating myocardium due to ischemic damage.

Key words: myocardial infarction, In-111-antimyosin antibody, scintigraphy, serum myosin light chain I, immunoradiometric assay

INTRODUCTION

CARDIAC MYOSIN is a basic structural protein of cardiac muscle that is abundant in myocytes, and consists of light chains I & II and a heavy chain. When the myocardium is injured by ischemia, cardiac myosin is continuously released into the bloodstream due to the destruction of myofibrillar proteins in the myocytes.[1–3] Antimyosin antibody can bind with the myosin in cardiac myocytes damaged by an ischemic event, and its uptake can be observed by means of nuclear medicine techniques.[4–8] Recently, two-site immunoradiometric assay (IRMA) with monoclonal antibody to cardiac myosin LCI was found to be a very useful technique for measuring of serum LCI concentrations as a marker of disease in patients with MI.[9] In addition, myocardial imaging with In-111-antimyosin monoclonal antibody Fab fragment (InAM) has been found to have both high sensitivity and specificity for detecting MI, not only in patients with acute infarcts, but also in those with subacute and chronic infarction.[4–8] However, the correlation between circulating serum levels of myosins and InAM uptake in the infarcted regions was not clear.

In this preliminary study, we compared myocardial imaging with InAM with the serum myosin LCI in patients with MI to evaluate whether the serum myocin LCI concentration is related to InAM uptake in the infarcted regions at the time of InAM injection.

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MATERIALS AND METHODS

Patients

We studied 17 patients who had been admitted to

our hospital for treatment for MI. They consisted of 14 men and 3 women ranging from 35 to 75 years of age (mean: 59.2 years). MI was diagnosed on the basis of precordial chest pain of at least 30 min duration, ECG changes (ST segment increase in two or more ECG leads), and a significant increase in cardiac enzyme activity. The time of infarction was determined by means of a routine combination of clinical, electrical, and enzymatic parameters. The interval from the onset of MI to evaluation ranged from 6 to 34 days (mean: 12.8 days). None of the patients had recurrence of chest pain or an increase in cardiac enzymes between the time of the acute episode and the time of the study.

Antimyosin antibody

Myocardial imaging was performed with an InAM (R11D10, Centocor Inc., Malvern, PA, USA), which was kindly supplied to us for clinical trials by Daiichi Radioisotope Labs., Ltd., Japan. After 5 m*l* of blood had been collected for measurement of the serum myosin LCI concentration, 74 MBq (2 mCi) of InAM was injected intravenously. Imaging was performed 48 hours later by planar views and single-photon emission computed tomography (SPECT) using both photopeaks (174 and 247 KeV) of indium-111. Informed consent was obtained from each patient before the study.

Instruments and image analysis

We used a SPECT system (Starcam 400 AC/T, GE, Milwaukee, WI, USA) with a medium energy collimator. SPECT data were acquired over 180° in 32 collection intervals of 30 sec, for a total imaging time of 17 min. The intensity of the InAM concentration in the myocardium was graded from zero to 3+ as follows: zero, no detectable uptake in the heart; 1+, myocardial uptake similar in intensity to that in bone marrow; 2+, myocardial uptake of lesser intensity than that in the liver; and 3+, myocardial uptake similar in intensity to that in the liver (Fig. 1). In this study, the uptake grades 1+, 2+, and 3+ were considered positive, while grade zero was considered negative. Myocardial InAM uptake ratios were calculated by comparison of the InAM activity in the infarct region to the lung background activity on the InAM Planar and SPECT images, respectively, using the average counts per pixel obtained from a ROI without attenuation correction. The background ROI was placed at a fixed distance from the heart border.

Serum myosin LCI assay

The serum myosin LCI concentration was determined with a Myosin LI "YAMASA" kit and monoclonal antibodies to human ventricular myosin LCI, kindly supplied by Nihon Medi-Physics Co., Japan. The following fundamental data for this two-site IRMA system were obtained by the usual assay procedure in our laboratory. The minimal detectable level of human ventricular myosin LCI was 0.42 ng/m*l* and cross-reactivity with human skeletal myosin light chain was 17.6%. No significant effect was observed when human ventricular myosin LCII, human atrial myosin LCI, human atrial myosin LCII, and human smooth muscle myosin light chain were added to the assay system. Multiple dilutions of serum from acute MI patients resulted in curves parallel to those obtained as standards for human ventricular myosin LCI. The recovery of human ventricular myosin LCI added to test serum was 111.5±6.2% (mean and SD), and the interassay coefficient of variation was 5.4%. The serum myosin LCI levels in normal subjects (n=50) ranged from 0.42 ng/m*l* to 2.2 ng/m*l*, and all control patients without myocardial disorders (n=30) had levels of less than 2.5 ng/m*l* (cut-off value).

RESULTS

The infarct area showed InAM uptake in all patients (100%); it was low intensity (1+) in 3 patients (17.6%) and significant (2+ or more) in the other 14 (82.4%). InAM uptake correlated with the infarct location as shown by ECG and CAG. Myocardial InAM uptake ratios of the 17 patients averaged 3.28 (range, 1.66–4.66), as shown in Table 1. In contrast, 12 of the 17 patients (70.6%) showed a serum myosin LCI concentration below the cut-off value, 5 having a concentration within the normal range (0.42–2.5 ng/m*l*) and 7 having levels below the detection limit (0.42 ng/m*l* or less). In addition, only 5 (29.4%) of the 17 patients showed elevated serum myosin LCI concentrations at the time of InAM injection, and these elevations were only slight, ranging from 3.4 to 4.5 ng/m*l* (mean: 3.75 ng/m*l*) (Table 1). As shown in Fig. 2, there was no significant correlation between the serum myosin LCI concentration and myocardial InAM uptake when patients were divided into three groups based on the serum myosin LCI concentration; i.e., 0.42 ng/m*l* or less (undetectable), 0.42–2.5 ng/m*l* (normal), and greater than 2.5 ng/m*l* (elevated).

DISCUSSION

Cardiac myosin is a major structural protein of the myocardium, which is abundant in cardiac myocytes, and consists of light chains I & II and a heavy chain. The cardiac myosin heavy chain has an important structural role, and the myosin light chains bind loosely with the heavy chain.[10] Thus, when the

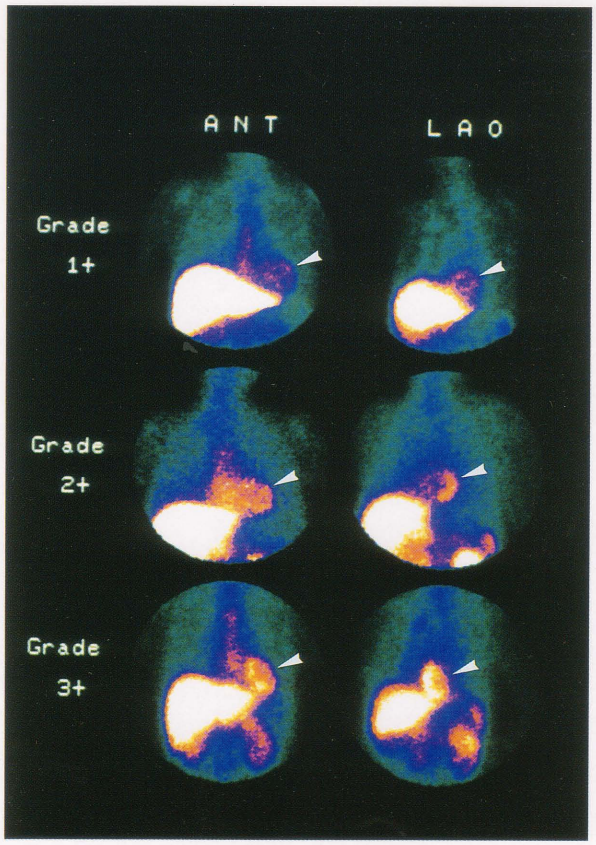

Fig. 1 The intensity of InAM concentration in myocardial tissue was graded from zero to 3+. The infarct area showed positive InAM uptake (1+ or more) in all patients.

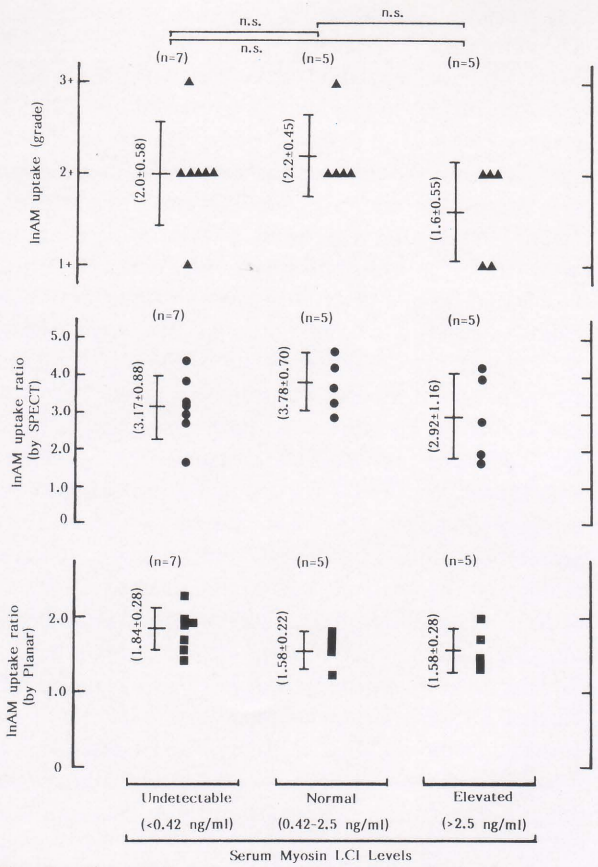

Fig. 2 Correlation between serum myosin LCI concentration and myocardial InAM uptake, InAM uptake ratios among patients divided into three groups based on concentration of serum myosin LCI.

Table 1 Results of InAM imaging compared with circulating serum myosin LCI concentration in 17 patients with myocardial infarction

Patients	Age/Sex	ECG location	Onset to injection (days)	InAM uptake (grade)	InAM location	InAM uptake ratio		Serum Myosin LCI (ng/ml)	CAG findings
						by Planar	by SPECT		
1US	58/M	A-L	34	2+	A	2.30	3.33	<0.42	LAD
2KK	61/M	I	6	2+	I	1.52	2.92	0.50	CIRC
3TH	70/M	A-L	8	2+	A*	1.96	3.27	<0.42	LAD
4AS	58/M	A-S	15	2+	A*	1.92	2.71	<0.42	LAD
5GS	48/M	A-S	10	2+	A	1.95	2.93	<0.42	LAD
6HS	59/M	I	12	2+	I	1.24	4.28	0.50	CIRC
7KK	65/M	I	14	1+	I	1.37	1.94	4.50	CIRC
8IY	61/M	A-L	15	2+	A#	1.83	3.32	0.50	LAD
9DS	60/F	A-S	6	2+	A	1.99	4.20	3.80	LAD
10YY	43/M	I-P	14	2+	P-L	1.60	3.71	0.70	CIRC
11KY	75/F	A	18	3+	A#	1.70	4.66	0.70	LAD
12IS	70/M	P	9	3+	P-L	1.72	4.46	<0.42	CIRC
13OT	76/M	I-L	13	2+	I	1.74	3.99	3.20	RCA
14UT	60/M	I	15	1+	I	1.32	1.66	4.00	RCA
15TS	60/F	I	7	1+	I	1.46	1.67	<0.42	RCA
16TT	35/M	A-S	12	2+	A	1.59	3.81	<0.42	LAD
17TF	48/M	A-L	9	2+	A*	1.47	2.82	3.40	LAD

* diffuse-type

\# doughnut-type

A=anterior; L=lateral; I=inferior; S=septal; P=posterior

LAD=left anterior descending artery; CIRC=left circumflex coronary artery; RCA=right coronary artery

myocardium is injured by ischemia, cardiac myosin is continuously released into the bloodstream,[1-3] and antimyosin antibody can bind with the cardiac myosin inside myocytes. *In vitro* studies of light chains I and II[1,3] and the heavy chain[2] of cardiac myosin have shown that their serum concentrations rise rapidly during an ischemic event and peak relatively slowly after the onset of MI, as late as one week or more after the onset. We have previously confirmed that the serum myosin LCI level rises rapidly, reaches its maximum at 2–6 days (mean: 4.55 days) after the onset of MI, and thereafter remains above the cut-off value for more than two weeks before returning to the normal range.[11] Recently, serum myosin LCI measurement by IRMA was found very useful for clinical monitoring in patients with acute MI.[9] The use of a radiolabeled antimyosin antibody for nuclear medicine imaging studies in MI patients was first suggested by Khaw et al.[12] They developed an antimyosin antibody for imaging, initially performing clinical studies with a Tc-99m-labeled antibody and later using an In-111-labeled diethyltriamine pentaacetic acid (DTPA)-antimyosin monoclonal antibody Fab fragment.[4,13,14] Recently, InAM has been used as a new myocardial imaging agent in clinical trials and has been found to have both high sensitivity and specificity for detecting infarcts not only in patients with acute MI, but also in those with subacute and chronic infarction.[4,5,7,8] However, the correlation between circulating serum concentration of myosins and InAM uptake in the infarcted regions in patients with MI remains to be clarified. Therefore, intentional and comparative assessment of serum myosin LCI levels with myocardial uptake of InAM was requested in patients after the onset of MI. Unfortunately, InAM cannot be obtained for routine use due to goverment restrictions at the present time. Thus, in a series of clinical trials of InAM, we compared myocardial uptake of InAM with the serum myosin LCI levels in patients with MI for preliminary evaluation of whether the circulating serum myosin LCI concentration is related to InAM uptake in the infarcted regions at the time of InAM injection. In the present study, our 17 patients had an interval from the onset of MI ranging from 6 to 34 days (mean: 12.8 days), and 12 of them had serum myosin LCI concentrations which were within the normal range or undetectable. Only 5 patients had an increased serum myosin LCI concentration at the time of InAM injection, and the increase was only slight, ranging from 3.4 to 4.5 ng/m*l* (mean: 3.77 ng/m*l*). However, the infarcted region showed signs of definite InAM uptake in all 17 patients.

In summary, these preliminary results indicate that even after the circulating serum myosin LCI level has decreased to normal, InAM can still bind to cardiac myosin in patients with MI, presumably until there is complete recovery from the hibernating myocardium due to ischemic damage, but further detailed and careful studies on the various degrees of MI in patients are needed.

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