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Increase in serum cardiac myosin light chain I associated with elective percutaneous transluminal coronary angioplasty in patients with ischemic heart disease

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Changes in serum myosin light chain I (MLCI) due to elective percutaneous transluminal coronary angioplasty (PTCA) were studied after PTCA (0, 8 and 48 hours) in 57 patients with old myocardial infarction (MI group) and 20 patients with angina pectoris (AP group). The AP group showed no increase after PTCA. In contrast, in the MI group there were 16 patients in whom MLCI at 48 hours was increased by 1.0 ng/m*l* or more (MI_1 group) and another group of 41 patients who showed no increase in MLCI (MI_2 group). The MI_1 group had a significantly higher incidence of (1) non-Q wave myocardial infarction (62.5% vs. 17.1%, $p<0.01$), (2) 99% stenosis of a coronary artery (50.0% vs. 12.2%, $p<0.01$), and (3) redistribution in a hypoperfusion area found in the delayed image of resting thallium-201 (^{201}Tl) myocardial scintigraphy (85.7% vs. 15.8%, $p<0.01$). The left ventricular ejection fraction (LVEF) was significantly improved in the MI_1 group, 3 to 4 months later (from 0.49 ± 0.12 to 0.58 ± 0.11, $p<0.01$), in contrast to the patient of MI_2 group who did not show any improvement. The AP group was not considered to have a bulk of myocardium impaired enough to show a release of MLCI due to PTCA-associated transient coronary occlusion. In the MI_1 group, however, MLCI was probably released from the chronically underperfused, but still salvageable, portion of the myocardium. This is consistent with the improvement in LVEF observed 3 to 4 months after the relief of severe coronary stenosis. These findings suggest that the MI_1 group had a large amount of "hibernating myocardium."

Key words: myosin light chain I, PTCA, hibernating myocardium

INTRODUCTION

MANY MARKERS of the degree of myocardial damage have been examined, including creatine kinase (CK), glutamate oxaloacetate transaminase (GOT), lactate dehydrogenase (LDH) and myoglobin (Mb). Recently it has become possible to measure serum levels of myosin light chain I (MLCI), a myocardial structural protein, as an indicator of myocardial necrosis. Serial changes in serum MLCI have been reported to be more useful in the assessment of myocardial infarct size than CK which can be released even in the case of solely enhanced permeability of the cell membrane.[1,2]

In experimental animals, it has been reported that an approximately 20 minutes coronary occlusion does not cause myocardial necrosis.[3–5] In humans, percutaneous transluminal coronary angioplasty (PTCA) provides a useful model in studying the myocardial damage due to a brief coronary occlusion. Changes in CK, CK-MB (MB isozyme of CK) and Mb associated with elective PTCA have been reported,[6–9] but to date, no studies on changes in MLCI have been published. To investigate PTCA-associated

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myocardial damage,[6,7] we studied changes in serum MLCI following elective PTCA and their possible pathophysiological significance.

MATERIALS AND METHODS

Patients

Seventy-seven patients who underwent successful PTCA were examined. The study group consisted of 57 patients with old myocardial infarctions who underwent PTCA on the infarct-related coronary artery (MI group), and 20 patients without previous myocardial infarction but with angina pectoris (AP group) (Table 1). There was no difference between the two groups in age, gender, the number of coronary lesions, location of the PTCA-targeted coronary artery, or the percentage of coronary stenosis.

Blood sampling

Peripheral blood samples were drawn four times: before PTCA, and immediately, 8 and 48 hours after PTCA. Serum MLCI, CK and Mb levels were determined.

Measurements of MLCI

Measurement of MLCI were made with the "Yamasa", Myosin LI Assay Kit (Nihon Medi-Physics Co., Hyogo, Japan), using an immunoradiometric assay (IRMA) with iodine-125 (^{125}I). For the measurement of radioactivity, a well-type scintilation counter (Auto well gamma system ARC-1000M, Aloka, Co., Tokyo, Japan) was used. The standard curve was provided with the kit (Fig. 1). To provide a standard curve for concentrations less than 2.5 ng/m*l*, standard solution was diluted to produce concentrations of 1.25, 0.625 and 0.313 ng/m*l*. Samples were incubated for 20 hours at 22°C. The detection limit of the system was 0.625 ng/m*l*. The coefficient of variation (CV) increased at the concentration of the standard solution less than 1.0 ng/m*l* (Fig. 2). The detection limit was comparable to those described by Suehiro et al.[10]

Table 1 Clinical features of the subjects studied

	Group MI (n=57)	Group AP (n=20)	p value
Age (yr)*	60.4±13.6	61.9±9.8	NS
Sex (M/F)	45/12	13/7	NS
Coronary lesions			
One-vessel	22	14	p<0.01
Multivessel	35 (61.4%)	6 (30.0%)	
Two-vessel	19	6	
Three-vessel	16	0	
Target coronary artery			
LAD	32	10	NS
LCX	7	2	NS
RCA	18	8	NS
Coronary % stenosis			
100%	10	0	NS
99%	13	1	NS
90%	23	11	NS
75%	11	8	NS

LAD=left anterior descending coronary artery; LCX=left circumflex artery; NS=not significant; RCA=right coronary artery. * Values are mean± standard deviation.

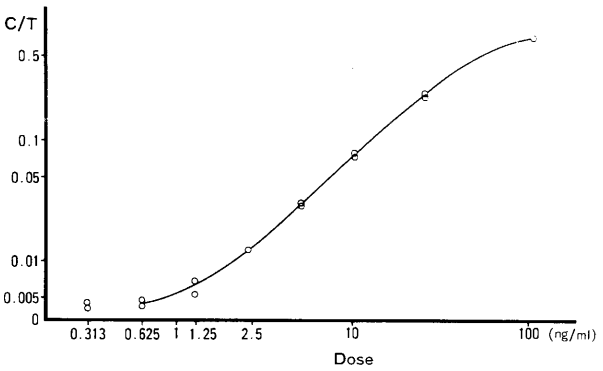

Fig. 1 Standard curve for measurement of MLCI (myosin light chain I). C=net binding count; T=total count.

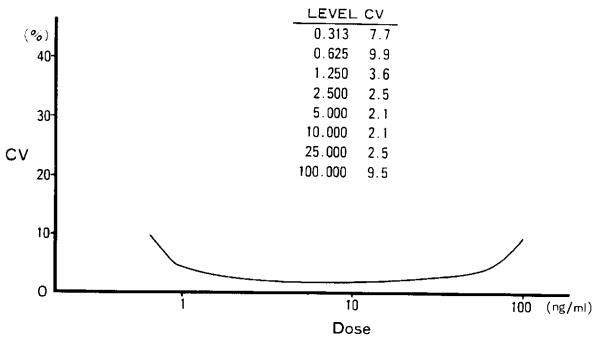

Fig. 2 Precision profile in this study. X axis indicates the logarithmic values of the concentration of the standard solution. CV=coefficient of variation.

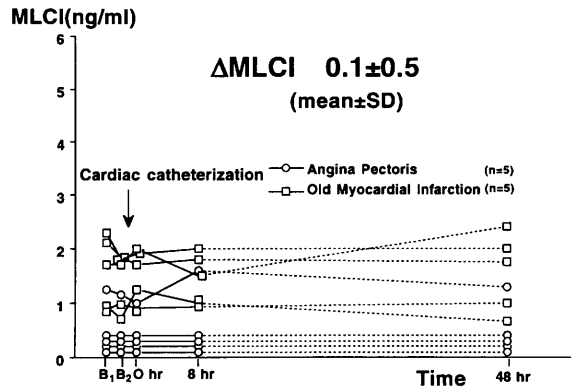

Fig. 3 Changes in MLCI (myosin light chain I) with cardiac catheterization. B=before PTCA; *Δ*MLCI= differences of MLCI between pre- and post-PTCA.

Examination of significant variations in MLCI
Changes in MLCI with cardiac catheterization were examined in five patients with old myocardial infarction and five patients with angina pectoris serving as control subjects (Fig. 3). The change in MLCI after catheterization was 0.1 ± 0.5 ng/ml (mean$\pm$SD; standard deviation). On the basis of this result, any change more than twice the SD, i.e., more than 1.0 ng/ml, was judged to be significant.

Factors examined
To clarify the factors which influence MLCI changes, the following factors were examined before PTCA: electrocardiogram (ECG) findings, the extent of stenosis of the PTCA-targeted coronary artery based on the classification of the American Heart Association, collateral circulation, and degree of myocardial wall motion abnormalities in the target area. PTCA balloon inflation time was taken as an index of the duration of the coronary occlusion.

Electrocardiographic evaluation
From the serial ECGs, all infarcts were classified as Q wave myocardial infarction (QMI) or non Q wave myocardial infarction (NQMI). The Diagnosis of QMI was based on Q waves 0.04 second or greater in duration and amplitude greater than 25% of following R wave, associated with evolving ST segment and T wave changes in the same lead. Q waves in lead III alone were not considered adequate for diagnosis of inferior wall Q wave infarction. In the case of posterior infarction, the presence of R waves 0.04 second or greater in duration with RV_1/SV_1 and/or RV_2/SV_2 greater than 1 associated with evolving ST segment and T wave changes in lead V_1 and/or V_2 was required. ECG criteria for NQMI included persistent ST or T wave changes without development of diagnostic Q waves.

Resting ^{201}Tl myocardial scintigraphy
Resting thallium-201 (^{201}Tl) myocardial scintigraphy was performed in 26 patients. The patients were injected intravenously with 148 MBq (4 mCi) of ^{201}Tl while seated. They were then placed supine on a scintigraphic imaging table. Single photon emission computed tomography (SPECT) imaging was carried out with a 180° imagings arc (45° right anterior oblique to 45° left posterior oblique) and 18 acquisitions of 50 second each. Data were acquired with a large field-of-view rotating gamma camera (ZLC-7500, Siemens Gammasonics, Inc., Chicago, USA) equipped with a high resolution collimator, and stored in an on-line computer system (Scintipac 2400, Shimadzu Co., Ltd., Kyoto, Japan). Initial and delayed myocardial imagings were carried out 10 minutes and 2 hours, respectively, after the injection of ^{201}Tl. Each projection was stored as a 64×64 matrix in a dedicated computer. The pixel size was adjusted so that the actual thickness of the slice was 6 mm/pixel. Six tomographic projection images (i.e. transverse, coronal, sagittal, vertical long axial, horizontal long axial and short axial) in each initial and delayed acquisition were reconstructed for visual interpretation, jointly by three experienced physicians. Redistribution was considered to have occurred when there was "filling in" of the defects or an improvement in the hypoperfusion in delayed SPECT images.

Cardiac catheterization
Coronary arteriograms were obtained in multiple projections by means of either Judkins or Sones technique. Left ventriculography (LVG) was performed at the projection of 30° right anterior oblique and 45° left anterior oblique for evaluation of abnormal wall motion and calculation of the left ventricular ejection fraction (LVEF). Wall motion abnormalities were classified into the following four: normal, reduced, none, dyskinetic without reference of the scintigraphic data. LVEF was calculated by the area-length method.[11] Grades of collateral filling from the contralateral vessel were: absent; poor=filling of side branches of the artery to be dilated via collateral channels without visualization of the epicardial segment; good=filling of the epicardial segment of the artery being dilated via collateral channels. The angioplasty procedure was performed by the femoral approach according to the standard technique. Balloon dilation catheters and guide wires of various sizes were used as clinically indicated. Angiographic success was defined as a final stenosis of less than 50%. None of the patients developed complications such as coronary dissection, acute coronary occlusion, side branch occlusion, or distal embolization. No perfusion catheter was used in any of the subjects.

In the 46 patients who were restudied 3 to 4 months after PTCA, LVG was done to assess the impact of revascularization. Restenosis was defined as a luminal narrowing of more than 75% at the previously dilated site.

Statistical analysis
Data are expressed as the mean$\pm$SD. Statistical comparisons were performed by appropriate t-test. Chi-square test and Fisher's exact test were also used to determined the significance of difference in observed rates of occurrence when appropriate. Namely, when the expected frequencies were less than five, Fisher's exact test was substituted. Differences of $p<0.05$ were considered significant.

RESULTS

Serial change in serum MLCI due to PTCA

No patient in the AP group had a significant increase in their serum MLCI level (Fig. 4). In the MI group, 16 of the 57 patients (28.0%) had an increase in serum MLCI of 1.0 ng/m*l* or more (from 1.3±1.0 to 3.1±1.2 ng/m*l*) after PTCA (Fig. 5): MI_1 group. The remaining 41 patients showed no significant increase: MI_2 group (Fig. 6). All of the patients in the MI_1 group had the highest serum MLCI at 48 hours among the three post-PTCA sera. When compared with pre-PTCA levels, MLCI increased by less than 1.0 ng/m*l* immediately and 8 hours after PTCA, but by 1.0 ng/m*l* or more 48 hours after PTCA.

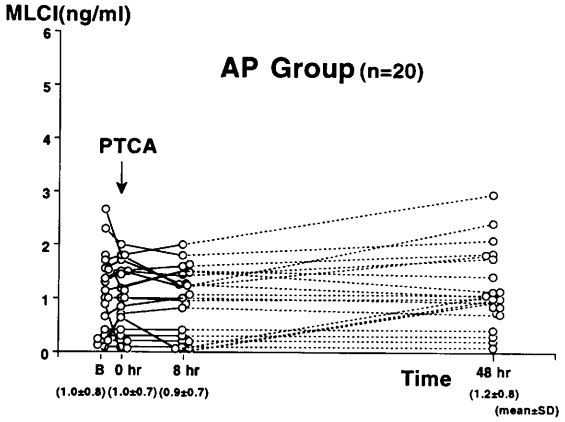

Fig. 4 Changes in MLCI (myosin light chain I) in the AP group. Values are mean±standard deviation. B=before PTCA.

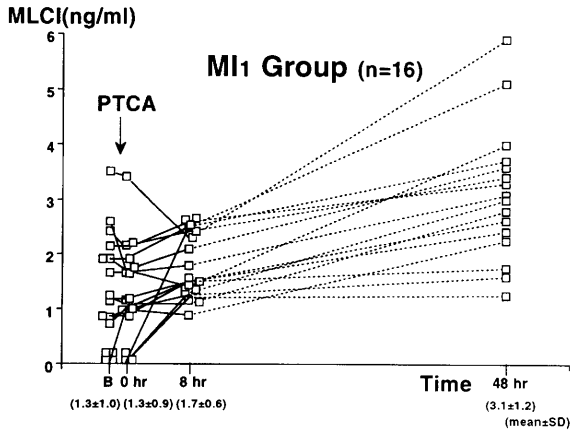

Fig. 5 Sixteen cases of PTCA-induced increase in MLCI (myosin light chain I) by more than 1.0 ng/m*l*. Values are mean±standard deviation. B=before PTCA.

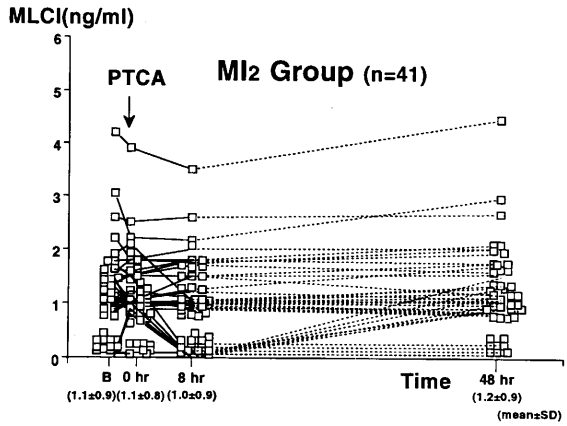

Fig. 6 Changes in MLCI (myosin light chain I) in the MI_2 group. Values are mean±standard deviation. B=before PTCA.

Clinical features of the MI_1 and MI_2 groups

Tables 2 and 3 show the clinical features of the MI_1 and MI_2 groups. There were no differences between the MI_1 and MI_2 groups in age, gender or length of time from the onset of myocardial infarction to elective PTCA. However, the MI_1 group contained significantly more patients with NQMI than the MI_2 group (10 of 16 (62.5%) vs. 7 of 41 (17.1%), $p<0.01$

Table 2 Comparison of clinical features between the MI_1 and MI_2 groups

	MI_1: ΔMLCI≧1.0 (n=16)	MI_2: ΔMLCI<1.0 (n=41)	p value
Age (yr)*	64.4±9.4	61.4±7.6	NS
Sex (M/F)	9/7	32/9	NS
Interval between AMI and PTCA (days)*	107±85	181±186	NS
ECG			
Q wave MI	6 (37.5%)	34 (82.9%)	p<0.01
non-Q wave MI	10 (62.5%)	7 (17.1%)	
T inversion	11 (68.8%)	20 (48.8%)	NS
Coronary % stenosis			
100%	0	10	NS
99%	8 (50.0%)	5 (12.2%)	p<0.01
90%	7	15	NS
75%	1	11	NS
Collaterals			
Absent	11	23	NS
Poor	4	4	NS
Good	1 (6.3%)	14 (34.1%)	NS
Wall motion (LVG)			
Normal	1	4	NS
Reduced	8	19	NS
None	6	14	NS
Dyskinetic	1	4	NS
(Aneurysmal)	(0)	(1)	
Inflation time of PTCA balloon (sec)*	394±192	453±329	NS
^{201}Tl scintigraphy redistribution	6/7 (85.7%)	3/19 (15.8%)	p<0.01

AMI=acute myocardial infarction; ECG=electrocardiogram; LVG=left ventriculography; MI=myocardial infarction; MLCI=myosin light chain I; NS=not significant; PTCA=percutaneous transluminal coronary angioplasty. *Values are mean±standard deviation.

Table 3 Summary of clinical characteristics of 16 cases in the MI_1 group

No.	Age/Sex	ECG	Target CA	Stenosis (%)	Collateral development	Wall motion (LVG)	^{201}Tl scintigraphy	MLCI (ng/m*l*) B/A	LVEF B/A
1	40/M	NQ	13	99	Absent	None	RD (+)	1.2/2.8	0.39/0.49
2	67/M	NQ	13	99	Absent	Reduced	RD (+)	1.7/3.1	0.47/0.59
3	64/M	NQ	7	99	Absent	Reduced	RD (+)	0.0/3.0	0.63/0.68
4	71/F	NQ	7	90	Good	Reduced	ND	2.1/3.3	0.48/0.69
5	78/F	NQ	11	90	Absent	Reduced	ND	1.9/4.0	0.61/0.69
6	57/M	Q	1	90	Poor	Reduced	ND	2.6/3.6	0.56/0.56
7	69/M	NQ	7	99	Absent	None	ND	0.0/1.3	0.55/0.59
8	56/F	Q	4	90	Absent	Dyskinetic	ND	0.0/3.7	0.24/0.33
9	56/F	Q	7	99	Absent	None	ND	3.5/5.9	0.33/0.51
10	74/F	Q	1	99	Absent	Reduced	ND	0.0/1.6	0.57/0.68
11	66/M	NQ	6	75	Absent	Reduced	ND	0.9/2.3	0.51/0.52
12	72/M	NQ	15	90	Poor	None	RD (+)	2.1/3.4	0.37/ND
13	63/F	Q	2	99	Poor	None	RD (+)	1.2/2.4	0.39/0.53
14	59/M	Q	2	90	Absent	Reduced	ND	1.9/5.1	0.65/0.69
15	78/F	NQ	7	99	Poor	None	RD (−)	0.9/2.6	0.36/0.48
16	61/M	NQ	6	90	Absent	Normal	RD (+)	0.7/1.8	0.54/0.74

A=after PTCA; B=before PTCA; CA=coronary artery defined by the American Heart Association committee report; ECG=electrocardiogram; LVEF=left ventricular ejection fraction; LVG=left ventriculography; MLCI=myosin light chain I; ND=not done; NQ=non-Q wave myocardial infarction; Q=Q wave myocardial infarction; RD=redistribution.

Table 4 Changes in serum CK and Mb during pre- and post-PTCA in the MI_1 group

	Before PTCA	After PTCA		
		0 hours	8 hours	48 hours
CK (IU/*l*)	67±30	59±20	107±53	89±43
Mb (ng/m*l*)	36±20	37±20	30±20	32±23

CK=creatine kinase; Mb=myoglobin; PTCA=percutaneous transluminal coronary angioplasty. Upper limit of normal is 195 IU/*l* in men and 180 IU/*l* in women for CK; 60 ng/m*l* for Mb. Values are mean± standard deviation.

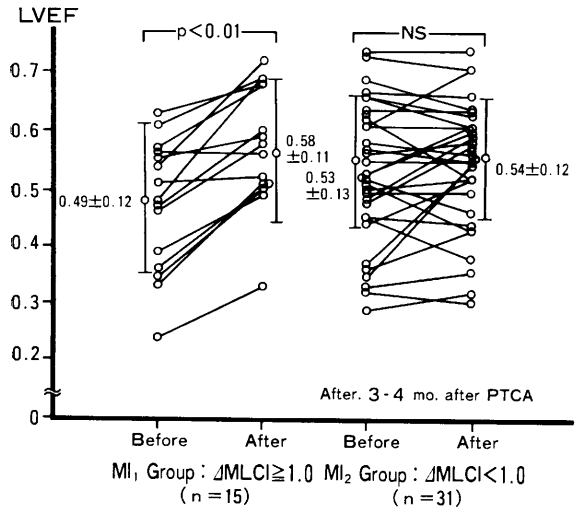

Fig. 7 Improvement of LVEF 3 to 4 months after PTCA in the MI_1 and MI_2 groups. "After" means 3 to 4 months after PTCA. Values are mean±standard deviation. LVEF=left ventricular ejection fraction; MLCI=myosin light chain I; NS=not significant.

by chi-square test). Stenosis of the PTCA-targeted coronary artery also differed, the MI_1 group had 99% stenosis more frequently than the MI_2 group (8 of 16 (50.0%) vs. 5 of 41 (12.2%), $p<0.01$ by Fisher's exact test). All of the 10 patients with 100% stenosis of the PTCA-targeted coronary artery belonged to the MI_2 group and had no changes in MLCI. There were no statistical differences in the degree of collateral circulation, the degree of pre-PTCA myocardial wall motion abnormalities or PTCA balloon inflation time.

^{201}Tl image and improvement in LVEF

On the delayed images with resting ^{201}Tl myocardial scintigraphy obtained in 26 patients, redistribution in the hypoperfusion area was noted in 6 of the 7 patients in the MI_1 group (85.7%), significantly more frequent than in the MI_2 group (3 of 19 patients, 15.8%, $p<0.01$ by Fisher's exact test) (Table 2).

Fifteen patients in the MI_1 group had a significant improvement in LVEF (from 0.49±0.12 to 0.58± 0.11, $p<0.01$). In 11 patients who did not develop restenosis, there was a 5% or greater improvement in LVEF. In the remaining 4 patients, LVEF improvement was less than 5% of pre-PTCA levels, and 2 of the 4 patients developed restenosis. In contrast, LVEF did not improve in the 31 patients in the MI_2 group (from 0.53±0.13 to 0.54±0.12) although only 1 patient developed restenosis (Fig. 7).

Correlation of change in MLCI with CK and Mb

None of the patients had abnormalities in CK or Mb values (Table 4).

DISCUSSION

Release of MLCI after PTCA

As to the PTCA for angina of effort, it has been reported that unstable angina, coronary spasm and intimal tear lead to the release of CK but that in successful PTCA, no release of CK was noted.[9] Measurement of CK-MB at 4 hour intervals after PTCA failed to demonstrate either complications or CK-MB release despite the high incidence of transient chest pain and ECG changes. It has therefore been reported that PTCA does not cause myocardial injury.[6] However, in their study with Mb, Pauletto et al.[7] noted the release of Mb as well as CK-MB, suggesting myocardial injury at the intramyocardial Mb structural level. Such divergence in the findings regarding the release of intramyocardial substances may be attributed to the following reasons: the changes in CK, CK-MB and Mb after PTCA are slight, if any; and the release reaches a peak in a very short time (4–8 hours for CK and 2–4 hours for Mb). We regard the changes in MLCI as a more reliable index of myocardial necrosis. This study demonstrated that MLCI increased in the MI group but not in the AP group.

In the AP group, no myocardial wall motion abnormalities were noted in the area dominated by the PTCA-targeted coronary artery. The patients appeared to have a "normal" myocardium. In these patients, MLCI did not increase significantly following PTCA, and this result is compatible with previous findings. In other words, this supports the hypothesis[3–5] that a brief (from several seconds to minutes) coronary occlusion associated with PTCA does not cause injury to the normal myocardium.

However, in the MI group, most of the patients had increased MLCI 48 hours after the PTCA-related brief coronary occlusion without detection of CK or Mb release. Whereas the AP group consisted almost entirely of patients with coronary stenosis of 90% or less, the MI group contained patients with 99% stenosis, and their myocardium was therefore thought susceptible to myocardial injury by PTCA. The release of MLCI may be attributable to myocardial injury due to (1) transient coronary artery occlusion, (2) reperfusion injury associated with relief of a severe stenosis, or (3) microembolism. If the release of MLCI occurs as described in the first hypothesis, this may correspond with the observation that MLCI increases approximately 48 hours after the onset of acute myocardial infarction.[1,2] However, in experimental infarction, it has been observed that MLCI release results from a decrease in myofibrillar ATPase activity about 48 hours after the start of ischemia.[12,13] It was also assumed that PTCA-associated localized lesions might lead to intracoronary thrombus formation. But, in view of the absence of cases with increased serum MLCI in the AP group, this possibility seems remote.

With elective PTCA in patients with 100% stenosis, no significant changes in MLCI were noted. The following reasons may be considered: myocardial necrosis was completed in the dominant area of 100% stenosis without any viable myocardium which can be saved with reperfusion therapy; the remaining myocardium was not so ischemic even if reperfusion was not conducted; or the PTCA-associated coronary occlusion was minor due to the development of collateral circulation.

Furthermore, the fact that MLCI increases regardless of the duration of the coronary occlusion suggests that the release of MLCI is related with the extent of stenosis in the targeted coronary artery and the condition of the myocardium. Two patients in the MI_1 group (Nos. 6 and 9 in Table 3) had high MLCI ($\geqq$2.5 ng/m*l*) before PTCA, and they might have had severe silent myocardial ischemia.

Possible pathophysiological significance

It has also been demonstrated that NQMI is closedly related to non-transmural and subendocardial infarction.[14] Ischemic areas that are not completely necrotized have been found in cases of NQMI.[15] This has been demonstrated by means of ^{201}Tl myocardial scintigraphy. Typically, it has been shown that ^{201}Tl redistribution scintigraphy appears to reliably distinguish viable from nonviable asynergic myocardial zones,[16,17] and predicts the response of these segments to coronary arterial bypass grafting[18,19] or PTCA.[20] Therefore, the myocardium of the MI_1 group subjects may contain predominantly viable muscle.

Furthermore, in the MI_1 group revascularization with PTCA had produced an improvement in LVEF when examined 3 or 4 months afterwards. Braunwald et al.[21] proposed the term "hibernating myocardium": ischemic myocardium results from months or years of ischemia and ventricular dysfunction persists until the blood flow is restored. The ischemia can be relieved with bypass surgery or coronary revascularization such as PTCA, followed by an improvement in systolic function. Cohen et al.[22] noted that successful PTCA was useful in salvaging chronic ischemic myocardium. The serum MLCI increased after PTCA was thought to be released from the chronically underperfused but still salvageable bulk of the myocardium.

Repeated ischemic episodes cause derangement of membrane permeability in the area perfused by the coronary artery with 99% stenosis.[4,9] This suggests that if coronary occlusion during PTCA results in new ischemia, intracellular dissociation of MLCI

is likely to occur. This hypothesis may be in disagreement with the theory of ischemic preconditioning.[23,24] However, in an animal experiment,[25] transient ischemia is produced by occlusion of the intact coronary artery. Therefore, the results of that experiment may not be identical to the hibernating myocardium. Although ischemic precondition in human beings has also been described,[24] the MI_1 group consisted mainly of patients with 99% stenosis of the coronary artery. Furthermore, it remains unclear whether the ischemic preconditioning exists in hibernating myocardium in the adjacent area to the infarcted myocardium.

It will now be important to examine when the hypoperfusion seen in ^{201}Tl myocardium scintigraphy improves after PTCA as compared with before PTCA and whether CK or Mb release can be detected in a shorter period of blood collection than in the present study.

CONCLUSIONS

In the MI group, 16 of the 57 patients (28.0%) had an increase in serum MLCI of 1.0 ng/m*l* or more after PTCA. There was a higher incidence of NQMI, 99% stenosis of the PTCA-targeted coronary artery, and redistribution in hypoperfusion areas in the delayed images with resting ^{201}Tl scintigraphy.

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