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Assessment of area at risk and efficacy of treatment in patients with acute coronary syndrome using ^{99m}Tc tetrofosmin imaging in humans

Hitoshi MATSUO,* Sachiro WATANABE,* Yoshio NISHIDA,* Tetsuo MATSUBARA,* Motoo KANO,* Akira SUGIYAMA,* Yukihiko MATSUNO,* Hiroshi ODA,* Yasunori KOTOO,* Hiroshige OOHASHI* Akira GOTO,** Kazunari MAKITA,** Hiroshi WATANABE,** Taketoshi MIZUTANI,** Hiroshi MIYAKE** and Takeyoshi IMAEDA***

**Division of Cardiology and Nephrology, Department of Internal Medicine*
***Department of Radiology, Gifu Prefectural Hospital*
****Department of Radiology, Gifu University, School of Medicine*

The determination of the myocardium at risk before intervention and the change in that region after intervention constitute a promising measurement tool for the assessment of acute therapy. A new ^{99m}Tc labeled myocardial blood flow tracer, ^{99m}Tc tetrofosmin, is expected to enable the evaluation of myocardium at risk because of the absence of redistribution. This preliminary study was performed in 9 patients with acute coronary syndrome (4 unstable angina and 5 acute myocardial infarction) to investigate whether recovery of perfusion by tetrofosmin imaging parallels mechanical improvement. Tetrofosmin imaging was performed acutely and 3–30 days later. Visual analysis of defect severity was assessed in both studies. Segments with improvement in perfusion were accompanied by significant wall motion recovery compared with normal and unimproved segments (Δ WMI: normal segments 0.40 ± 0.67, improved segments 1.79 ± 0.68, unimproved segments -0.15 ± 0.16, $p<0.01$ for improved segments compared with other groups), suggesting the efficacy of this tracer for the assessment of the acute therapy. These data suggest that ^{99m}Tc tetrofosmin imaging is a useful method for the assessment of the myocardial area at risk and the efficacy of acute therapy in acute myocardial infarction and unstable angina.

Key words: ^{99m}Tc tetrofosmin, acute myocardial infarction, unstable angina, area at risk, PTCA

INTRODUCTION

A METHOD to assess the extent of jeopardized myocardium during acute coronary ischemic episodes would be of clinical interest and provide very important information for the treatment of patients with acute myocardial infarction and unstable angina.[2,3] New ^{99m}Tc labeled myocardial blood flow tracers such as ^{99m}Tc-hexakis-2-methoxy-isobutyl-isonitrile (isonitrile)[4,5] and ^{99m}Tc-1,2-bis[bis (2-ethoxyethyl)phosphino]ethane (tetrofosmin)[6–9] are expected to enable an evaluation of myocardium at risk because of the absence of redistribution. The ability to assess the extent of myocardium at risk during early myocardial infarction with ^{99m}Tc isonitrile has already been demonstrated in an animal model[10] and in clinical trial.[11–14] This study is the first report concerning the efficacy of ^{99m}Tc tetrofosmin as a tracer for the assessment of perfusion abnormality in acute coronary syndrome.

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For reprints contact: Hitoshi Matsuo, M.D., Gifu Prefectural Hospital, 4–6–1 Noishiki, Gifu City, Gifu Prefecture 500, JAPAN.

SUBJECTS AND METHODS

Patients

Nine patients who suffered from acute coronary syndrome (5 unstable angina and 4 acute myocardial infarction) were enrolled in this study. Patient selection was based on the following criteria.

1) Frequent or persisting chest pain within 8 hours. 2) Electrocardiographical evidence of myocardial ischemia or acute infarction. 3) Gamma camera system availability at the time of the patient's arrival. As shown in Table 1, 8 of 9 patients had critical stenosis in the relevant lesion, and the flow was restored in the catheterization laboratory by direct percutaneous transluminal coronary angioplasty or thrombolysis.

Preparation of ^{99m}Tc tetrofosmin

This radiopharmaceutical was supplied in kit form (Amersham Japan, Tokyo). About 555 to 700 MBq of ^{99m}Tc in 1 to 3 m*l* of 0.9% NaCl was added to the vial. The vial was then shaken and left at room temperature for 15 minutes. 555 MBq of tetrofosmin was injected in each patients without any delay of catheterization.

^{99m}Tc tetrofosmin imaging

555 MBq of ^{99m}Tc tetrofosmin was injected into all patients before the emergency catheterization. Because of the minimal redistribution of this radionuclide, tomographic imaging was performed 1–6 hours later, after intervention. A second injection and acquisition were performed at 3–30 days after acute phase catheterization with a rotating gamma camera (ZLC-7500, Siemens Co. Ltd.). Thirty-two images were acquired for 30 seconds over a 180° arc, beginning with a 45° right anterior oblique and ending at a left posterior oblique view.

^{99m}Tc tetrofosmin imaging was processed in a computer (Scintipac 7000, Shimadzu Co. Ltd.). Standard back projection algorithm and Shepp and Logan filter were used to reconstruct the images. Transaxial slices were then reconstructed and realigned into frontal and saggital sections with the manufacturer's software.

SPECT data analysis

The left ventricle was divided into 9 segments as shown in Fig. 1. Tracer uptake of 162 segments in 18 SPECT studies was assessed visually by 2 observers independently. Perfusion defects were classified into 4 grades (0: normal, 1: mild defect, 2: moderate defect, 3: severe defect). Agreement between observers concerning the defect score was obtained for 95% of all segments (154 segments/162 segments).

Table 1 Individual patients data

Patient initials	Age	Sex	Clinical diagnosis	coronary finding	Intervention	Elapsed time	CPK peak	LVEF acute	LVEF chronic
NS 1	77	M	UAP(AT)	LAD SEG 9 : 99%	PTCA(99%➡25%)	UC	NE	85.4	83.3
NS 2	69	F	UAP(AS)	normal	not done	24	NE	32.7	66.1
FS 1	54	F	UAP(AS) OMI(PT)	LAD SEG 6 : 99%	PTCA(99%➡25%)	UC	NE	38.4	52.4
KM	68	F	UAP(AS)	LAD SEG 6 : 99% LCX SEG 13 : 75%	PTCA(99%➡50%)	3.0	NE	—	75.0
YR	80	F	UAP(AS) OMI(PT)	LAD SEG 7 : 99% RCA SEG 3 : 90% LCX SEG 13 : 100%	PTCA(99%➡50%) PTCA(90%➡25%)	5.0	NE	—	—
AM	69	F	AMI(INF)	RCA SEG 1 : 99% LAD SEG 7 : 90%	PTCA(99%➡25%)	30	826	—	61.9
FS 2	72	F	AMI(AS)	LAD SEG 7 : 99%	PTCA(99%➡50%)	2.5	NE MLC↑3.9	48.3	85.2
TS	61	M	AMI(AS) OMI(PT)	LAD SEG 7 : 100% LCX SEG 13 : 100%	PTCA(100%➡25%)	4.0	4030	—	38.5
SS	59	M	AMI(AS)	LAD SEG 7 : 50% SEG 8 : 100%	PTCR(100%➡99%)	3.0	1218	52.4	70.9

M: man, F: woman, UAP: unstable angina, AMI: Acute myocardial infarction, AT: anterior, AS: anteroseptal, PT: posterior, INF: inferior, LAD: left anterior descending artery, RCA: right coronary artery, LCX: left circumflex artery, SEG: segments according to the AHA classification, PTCA: percutaneous transluminal coronary angioplasty, PTCR: percutaneous transluminal coronary thrombolysis, LVEF: left ventricular ejection fraction, UC: unclear, NE: no elevation above normal range, MLC: myosin light chain.

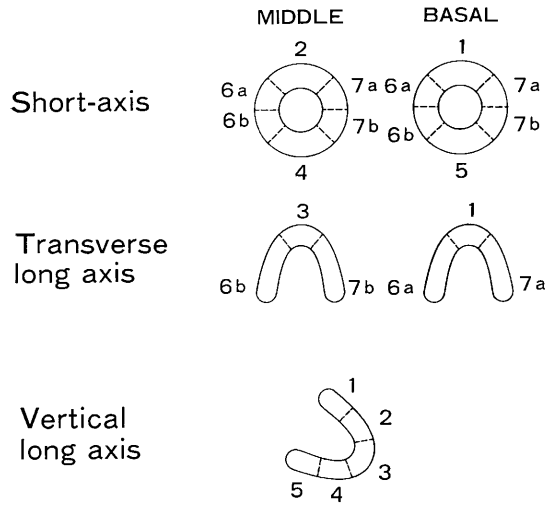
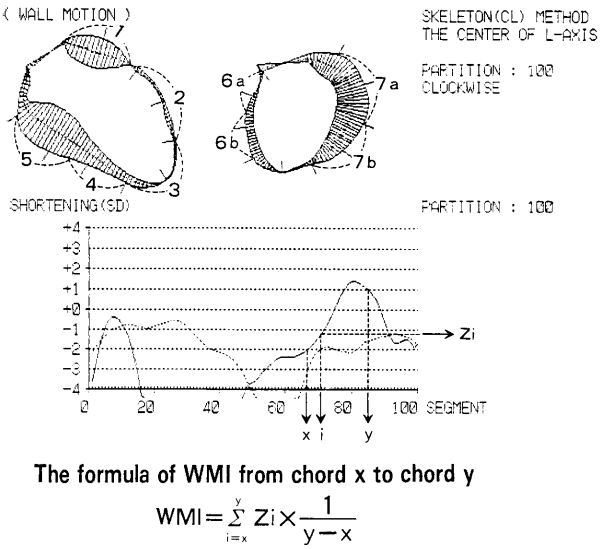


Fig. 1 Representation of SPECT imaging. The left ventricle were divided into 9 major regions.



The formula of WMI from chord x to chord y

$$WMI = \sum_{i=x}^{y} Zi \times \frac{1}{y-x}$$

Fig. 2 The formula calculating the wall motion index. Biplane left ventriculogram were divided into the 9 regions for comparison with perfusion. See text in detail.

As for the 8 segments without agreement, the observers reached a final judgement by discussion. The sum of the defect scores of 9 segments was calculated in each SPECT study, and defined as the total perfusion defect score. A comparison of the defect scores for the image with tracer injection before intervention and that after intervention was made, and then all segments were divided into normal, improved, and unimproved perfusion segments.

Left ventricular wall motion analysis

Biplane left ventriculography was performed during an emergency catheterization study in 5 of 9 patients, and during chronic catheterization in 8 of 9 patients. Therefore, the difference of wall motion in acute and chronic (Δ WMI) was analysed in only 5 of 9 patients, and the relationship of perfusion to chronic wall motion were assessed in 8 of 9 patients.

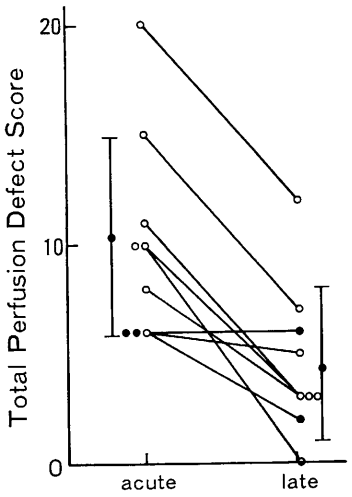


Fig. 3 Total perfusion defect score in the acute and late stages of infarction in 9 patients with acute coronary syndrome.

○ Anteroseptal lesion, ● Other lesion. Acute: ^{99m}Tc Tetrofosmin injection before emergent catheterization. Late: ^{99m}Tc Tetrofosmin injection 3–30 days after emergency catheterization.

Cine films were projected and end-diastolic and end-systolic endocardial contours were traced from the frames with maximum and minimum volume, respectively, from a normal non-postpremature sinus beat. Wall motion was measured by the centerline method along 100 chords constructed perpendicular to a centerline drawn midway between the end-diastolic and end-systolic contours, normalized for heart size, and expressed in units of standard deviation from the mean motion in 20 normal subjects. The segmental wall motion index was calculated as the mean motion of chords lying within the segments as described in Fig. 2 and expressed in SD per chord.

Statistical analysis

Data were statistically compared using Student's t test for paired samples for the total perfusion defect score. Analysis of variance (ANOVA) was used for the comparison among normal, improved, and unimproved perfusion segments. Linear correlations were performed between the total perfusion defect score and left ventricular ejection fraction. A p value of <0.05 was considered a significant difference.

RESULTS

Demonstration of reversible perfusion defects

Distinct ischemic perfusion defects present in acute

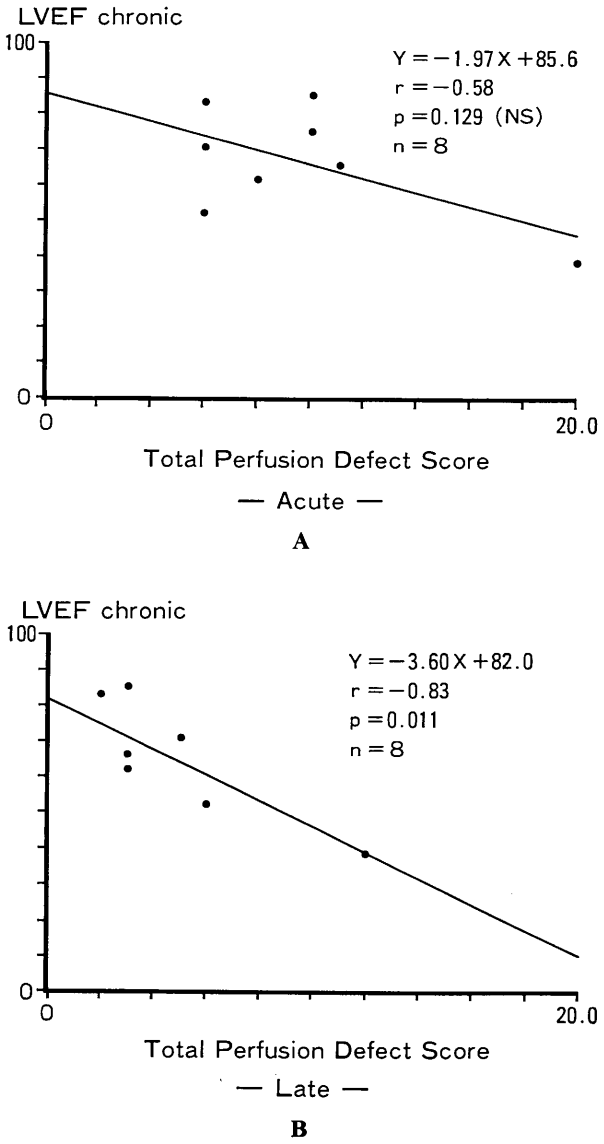


Fig. 4 Correlation between acute (panel A), late (panel B) total perfusion defect score and left ventricular ejection fraction chronic. Only late total perfusion score correlated with LVEF at chronic.

images were reduced in late images in 8 of 9 patients, as shown in Fig. 3. No difference was observed in one patient with inferior myocardial infarction (case AM).

Relationship between the defect severity and left ventricular function

Although the total perfusion defect score of chronic images correlated inversely with ejection fraction in the chronic phase ($p=0.011$), no correlation was found between the total perfusion defect score for acute images and the ejection fraction obtained at chronic (Figs. 4A, 4B). The relationship between the severity of the perfusion defect and wall motion

Table 2 The relationship between the perfusion defect severity and wall motion abnormality

A: Wall motion index at acute ventriculography vs. perfusion defect severity on acute images.

		PERFUSION DEFECT SCORE(acute)			
		Normal	Mild	Moderate	Severe
WMI(acute) n=45	-2.0<WMI	24/30	1/2	2/5	2/8
	WMI≦-2.0	6/30	1/2	3/5	6/8
	%asynergy	29.0%	50.0%	60.0%	75.0%

B: Wall motion index at chronic ventriculography vs. perfusion defect severity on acute images.

		PERFUSION DEFECT SCORE(acute)			
		Normal	Mild	Moderate	Severe
WMI(chronic) n=72	-2.0<WMI	39/40	4/4	9/14	9/14
	WMI≦-2.0	1/40	0/4	5/14	5/14
	%asynergy	2.5%	0.0%	35.7%	35.7%

C: Wall motion index at acute ventriculography vs. perfusion defect severity on chronic images.

		PERFUSION DEFECT SCORE(chronic)			
		Normal	Mild	Moderate	Severe
WMI(acute) n=45	-2.0<WMI	26/36	3/6	0/1	0/2
	WMI≦-2.0	10/36	3/6	1/1	2/2
	%asynergy	27.8%	50.0%	100.0%	100.0%

D: Wall motion index at chronic ventriculography vs. perfusion defect severity on chronic images.

		PERFUSION DEFECT SCORE(chronic)			
		Normal	Mild	Moderate	Severe
WMI(chronic) n=72	-2.0<WMI	51/54	8/12	0/1	1/5
	WMI≦-2.0	3/54	4/12	1/1	4/5
	%asynergy	5.6%	33.3%	100.0%	80.0%

index obtained in the acute and chronic phases is shown in Tables 2A and 2B. Severe asynergy, defined as a WMI less than −2.0 SD/chord, was observed by acute phase left ventriculography in 75.0% of the segments with severe perfusion defects on acute images, but only 36.7% of the segments with severe defects on acute images were judged as severe asynergy by chronic phase left ventriculography, suggesting that acute images reflect pretreatment

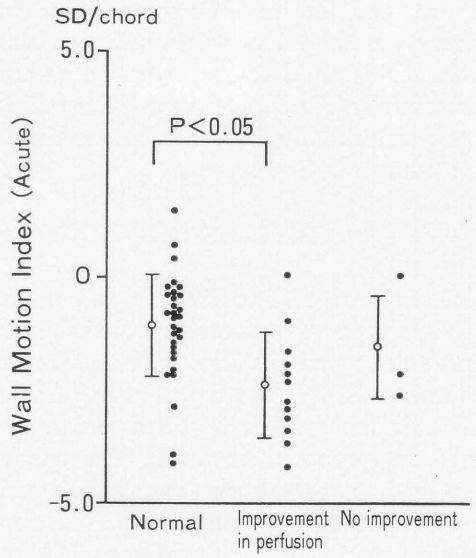


Fig. 5 Scatter plots showing comparison of wall motion index of acute phase and the pattern of perfusion change from acute to subacute assessed by ^{99m}Tc tetrofosmin uptake.

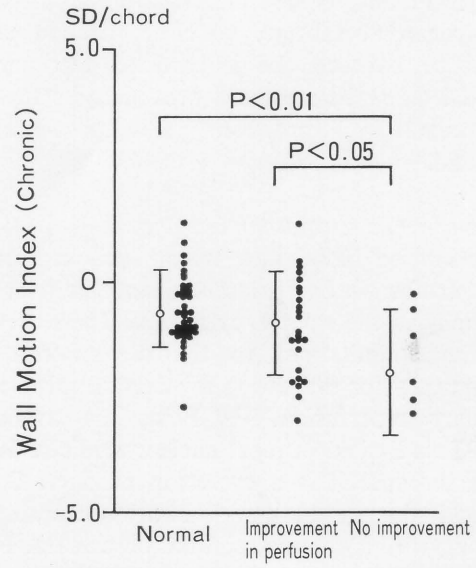


Fig. 6 Scatter plots showing comparison of wall motion index of chronic phase and the pattern of perfusion change from acute to subacute assessed by ^{99m}Tc tetrofosmin uptake.

perfusion. On the other hand, perfusion defects on the late images reflected wall motion abnormality in the chronic phase rather than the acute phase, as shown in Tables 2C and 2D.

Relationship between perfusion defect change and wall motion score

The relationship between acute phase wall motion and the change in tracer uptake is shown in Fig. 5.

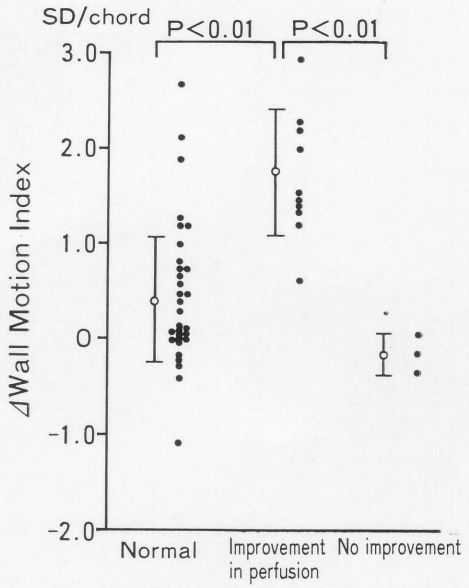


Fig. 7 Scatter plots representing the wall motion recovery (Δ WMI) in relation to the perfusion change assessed by ^{99m}Tc tetrofosmin imaging.

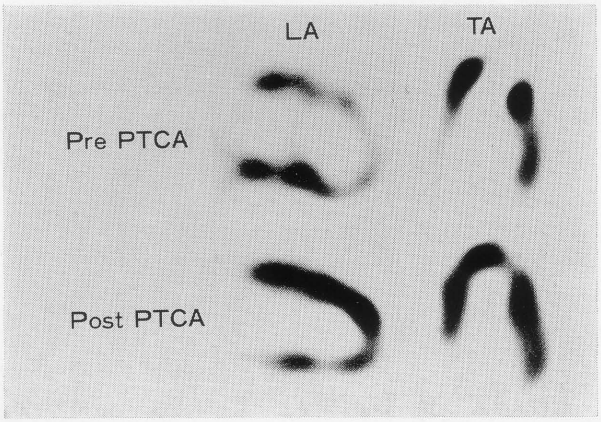


Fig. 8 Representative ^{99m}Tc tetrofosmin tomographic images from patient FS 2. Upper two slices with tracer injection just before PTCA to the proximal portion of LAD showing perfusion defect of anteroseptal wall. The lower two slices with tracer injection 3 days after PTCA, showing perfusion improvement in infarcted region. LA: long axis view. TA: transaxial view.

Segments with improvement in perfusion showed significantly worse wall motion in the acute phase than normal segments (Normal: -1.01 ± 1.15, Improved: -2.38 ± 1.14, Unimproved: -1.52 ± 1.15, $p<0.05$ Normal vs. Improved). But this difference was obscured in the chronic phase (Normal: -0.62 ± 0.67, Improved: -0.95 ± 1.13, Unimproved: -1.98 ± 1.34, $p<0.01$ for segments with no improvement vs. other groups) suggesting that mechanical improvement was obtained parallel to the perfusion improvement (Fig. 6). Figure 7 showed that segments

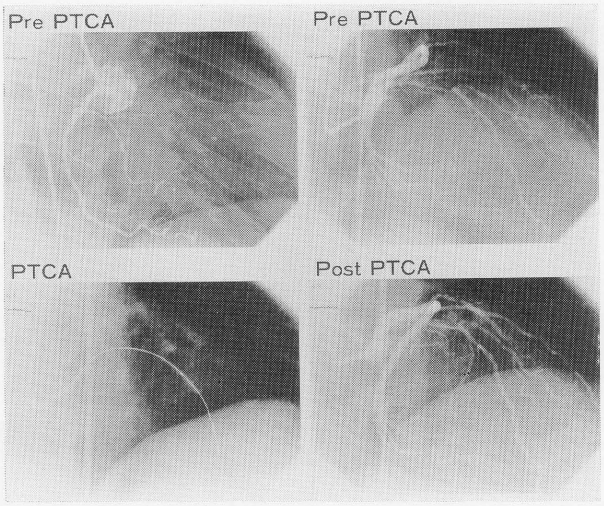


Fig. 9 Coronary angiogram of patient FS 2. 99% severe stenosis of proximal portion of left anterior descending artery with no other stenosis was shown in upper panel. PTCA was performed immediately and successfully as shown in lower panel.

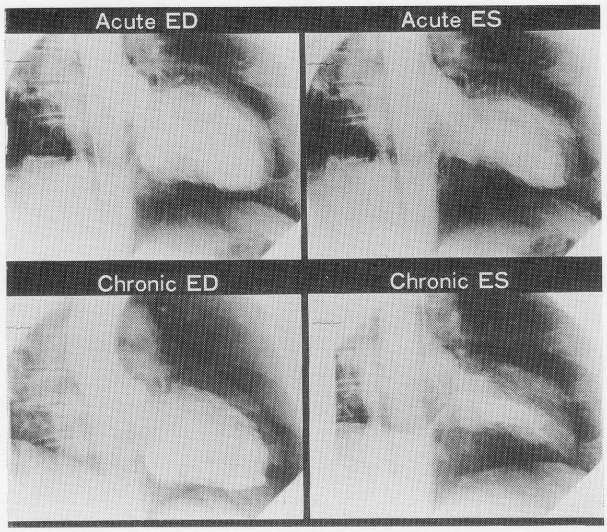


Fig. 10 Left ventriculography of patients FS 2. Upper panel showing the end-diastolic (left) and end-systolic (right) frame of acute phase left ventriculography. Lower panel showing the end-diastolic and end-systolic frame of left ventriculography at 1 month after PTCA. Significant improvement of wall motion is clearly demonstrated.

with improved perfusion also had significantly higher functional recovery than normal and unimproved segments, showing the effects of revascularization (Normal: 0.40 ± 0.67, Improved: 1.79 ± 0.68, Unimproved: -0.15 ± 0.16).

Case presentation

Representative serial tomographic imaging of ^{99m}Tc tetrofosmin is shown in Fig. 8. 99% severe stenosis of the proximal portion of the left anterior descending artery was the relevant lesion in this case with unstable angina. PTCA was performed immediately and successfully (Fig. 9). Left ventricular wall motion improved significantly from the acute to the chronic phase as shown in Fig. 10.

DISCUSSION

The effectiveness of thrombolytic and mechanical reperfusion therapy in acute myocardial infarction and unstable angina has already been demonstrated by several trials,[15–20] but the assessment of results in the individual patient is still a major problem. Among the proposed methods, the comparison of pre- and post-treatment myocardial perfusion images is particularly attractive. This approach would allow us to identify the extent of the residual damage after intervention, which has an important prognostic value.[15–17] Furthermore, it would be possible to recognize the amount of myocardium at risk before treatment, which can be very different even in patients with occlusion of the same coronary artery.[3] Finally, in this reperfusion era, the degree of myocardial salvage, which is defined as the difference between the jeopardized territory and residual damaged area, has proved to be the main determinant of prognosis and post-infarction ischemia.[21]

Value of ^{99m}Tc tetrofosmin imaging

^{99m}Tc labeled blood flow tracer such as isonitrile and tetrofosmin has several advantages over ^{201}Tl especially in the emergency setting. There are some significant limitations to the use of rest ^{201}Tl scintigraphy for evaluating myocardial salvage after coronary reperfusion.[22,23] First, the availability of ^{201}Tl is limited in most nuclear medicine laboratories, because it is a cyclotron product. Second, physical characteristics of ^{201}Tl are not optimal for imaging with a gamma scintillation camera. Finally and most importantly, because of prominent redistribution, it is necessary to obtain pretreatment images which may delay for up to 20–30 minutes the institution of thrombolytic therapy. ^{99m}Tc blood flow agent solves all of the above problems. Although many investigaters demonstrated the feasibility and utility of ^{99m}Tc isonitrile for the assessment of the area at risk and the efficacy of the treatment of acute myocardial ischemia, our study is the first preliminary report to demonstrate the usefulness of ^{99m}Tc tetrofosmin imaging for the assessment of the efficacy of interventional therapy in an emergency setting. By comparison with ^{99m}Tc isonitrile, ^{99m}Tc tetrofosmin shows similar heart uptake and retention and blood clearance kinetics but signifi-

cantly faster clearance from both lung and liver, offering the possibility of earlier imaging or higher quality images at a comparable imaging time and with a favorable dosimetric pattern.[7,24] In addition, the labeling procedure for tetrofosmin, which is allowed to stand at room temperature for 15 minutes, is much easier than that of isonitrile which requires a 15 minute boiling procedure in the water bath and a cooling process. These differences may be the principal advantages of tetrofosmin over isonitrile especially during emergency use. Similar to the study with ^{99m}Tc isonitrile, we observed the reduction of defect size with successful reperfusion. The segments with improved tracer uptake are accompanied by functional recovery, which should be regarded as the best end point for assessing the results of acute intervention.

Study limitation

There are several limitations to this study. First, because it covers only a small number of patients, further evaluation is necessary with a larger population. Second, the mechanism of this tracer uptake is unknown, and basic research on the uptake mechanism is necessary. Third, no data about tracer kinetics with reperfusion models have been reported. By overcoming these limitations, the differences and respective advantages of isonitrile and tetrofosmin will become clear, and the most useful strategy for the assessment of acute interventional therapy will be evident.

Conclusion

This study demonstrated the potential role of ^{99m}Tc tetrofosmin imaging for the assessment of the area at risk and the effect of acute interventional therapy in patients with acute coronary syndrome.

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