Prediction of Salvaged Myocardium in Patients with Acute Myocardial Infarction after Primary Percutaneous Coronary Angioplasty using early Thallium-201 Redistribution Myocardial Perfusion Imaging

Joon Young Choi, M.D., You-Jung Yang, M.D., Seung Jin Choi, M.D., Jeong Seok Yeo, M.D., Seong-Wook Park[1], M.D., Jae-Kwan Song[1], M.D., Dae Hyuk Moon, M.D.

Departments of Nuclear Medicine and Internal Medicine[1], Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

급성심근경색증의 일차적 관동맥성형술 후 조기 Tl-201 재분포영상을 이용한 구조심근 예측

최준영, 양유정, 최승진, 여정석, 박성욱[1], 송재관[1], 문대혁

울산대학교 의과대학 서울아산병원 핵의학과, 내과[1]

국문초록

목 적 : 심근경색증 후 재관류술에 의해 구조된 심근의 범위는 중요한 예후 인자중의 하나이다. 급성심근경색증의 일차적 관동맥성형술 후 조기 Tl-201 재분포영상이 구조심근과 심근벽운동 호전을 예측할 수 있는지 알아보았다. **대상 및 방법** : 흉통 발생 5.2±2.8시간에 급성심근경색증으로 일차적 관동맥성형술을 시행한 36명을 대상으로 관동맥성형술 후 5.8±2.1일에 디피리다몰 부하 - 4 시간 재분포 Tl-201 SPECT 영상을 얻었다. Tl-201 재분포 영상은 좌심실을 16분절로 나누고, 각 분절의 섭취를 5등급으로 평가하였다. 심초음파는 내원 당시, 경색 후 7일, 30일, 7개월에 시행하였고, 구조심근 분절은 내원 당시 심초음파상 벽 운동 이상이 있으면서 30일 또는 7개월 심초음파에서 벽 운동이 호전된 분절로 정의하였다. **결 과** : 내원 당시 212분절에서 벽 운동 이상을 보였다(저운동 41분절, 무운동 171분절). 이 중 1개월에는 78분절(36.8%)에서, 7개월에는 97분절(45.8%)에서 벽 운동이 호전되어 구조심근으로 판정하였다. 구조심근을 찾는 Tl-201 재분포 영상의 수신자판단특성곡선면적은 1개월에 대해서는 0.79±0.03, 7개월에 대해서는 0.83±0.03이었다. Tl-201 섭취 40%를 경계로 정할 때 재분포 영상의 구조심근을 찾는 예민도, 특이도는 1개월에서는 84.6%(66/68), 55.2%(74/134), 7개월에서는 87.6%(85/97), 64.3%(74/115)였다. 재분포영상에서 Tl-201의 섭취정도와 벽 운동의 호전될 확률은 서로 비례하는 경향을 나타내었다. **결 론** : 급성심근경색증의 일차적 관동맥성형술 후 10일 이내에 시행한 조기 Tl-201 재분포영상은 구조심근과 심근벽운동 호전 예측 판정에 높은 예민도로 유용하게 사용될 수 있는 검사이다.

Key Words : Thallium-201, myocardial perfusion SPECT, acute myocardial infarction, primary percutaneous transluminal coronary angioplasty

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Corresponding Author: Dae Hyuk Moon, M.D.

Department of Nuclear Medicine, Asan Medical Center, University of Ulsan College of Medicine,

388-1 Pungnap-dong, Songpa-gu, Seoul 138-736, Korea

Tel: 82-2-3010-4592 / Fax: 82-2-3010-4588

E-mail: dhmoon@amc.seoul.kr

Introduction

Reperfusion therapy using either intravenous thrombolytic therapy or primary percutaneous transluminal coronary angioplasty (PTCA) is an established therapy for acute myocardial infarction (MI) to allow prompt restoration of coronary blood flow to jeopardized myocardium.[1] Primary angioplasty for patients with acute MI has been shown in randomized trials to be a very effective reperfusion therapy, and high rates of complete and sustained patency have been reported.[2,3] However, the angiographic demontration of vessel patency after reperfusion dose not necessarily reply effective reflow or actual myocardial salvage within the infarcted area.[4,5] Futhermore, because of myocardial stunning, regional wall motion abnormalities persist, despite early recanalization.[6] Therefore, various imaging techniques have been proposed to assess the effectiveness of myocardial reperfusion in acute MI.

Several approaches are currently used for this aim. The first is based on the demonstrated relationship between recognition of tissue viability in dysfunctioning segments and subsequent spontaneous recovery. This is usually considered as "golden standard" for myocardial viability.[7-9] The other is based on the prediction of late functional recovery of asynergic regions by means of inotropic stimuli, mainly by using low-dose dobutamine echocardiography.[7,10] The demonstration of microvascular integrity within a reperfused infarcted area by myocardial contrast echocardiography has been found to be a requisite of tissue viability, and consequently, a possible indirect sign of effective reperfusion and a potential predictor of late functional recovery,[11,12] although it needs to inject contrast agents in the coronary artery and might be less accurate than myocardial perfusion imaging.[13] Assessment of myocardial viability may be performed with metabolic imaging with positron emission tomography,[7,8] but because of its limited availability, myocardial perfusion imaging with single-photon tracers is more frequently used.[9,13,14] In particular, Tc-99m sestamibi myocardial perfusion imaging has been extensively used in this field, mainly because of the possibility to directly evaluate the extent of tissue salvage by comparing pre-perfusion and post-reperfusion images.[13,14] There were relatively fewer studies reporting the detection of myocardial salvage by Tl-201 myocardial perfusion imaging.[9,15,16] Futhermore, no previous reports have demonstrated the accuracy of Tl-201 myocardial perfusion imaging for detecting salvaged myocardium in patients with acure MI after reperfusion by segmental basis for the comparison with echocardiographic wall motion recovery.

The present study was designed to investigate if single-photon emission computed tomography (SPECT) with Tl-201 performed early within 10 days after reperfusion can be used to predict the salvaged myocardium and functional recovery during the 7 months following primary PTCA in patients with acute MI.

Materials and Methods

1. Subjects

We prospectively studied patients with first acute MI who underwent successful primary PTCA within 12 hr after the onset of chest pain during a 12-month study period. Inclusion criteria for the study were 1) chest pain>30 min in duration and presentation within 12 hr after the onset of symptoms, 2) ST-segment elevation>0.1 mV in two contiguous electrocardiographic leads and 3) successful primary angioplasty (Thrombolysis In Myocardial Infarction [TIMI] flow grade.[17] Exclusion criteria were valvular heart disease, inadequate quality of

echocardiographic image, atrial fibrillation or prior history of revascularization.

Of 48 patients who matched the selection criteria, 10 did not adhere to the follow-up protocol. Later, two patients were excluded due to reinfarction. The final study subjects were 36 patients (27 men and 9 women; age range 28-74 yr; mean age 58 yr).

Blood samples for the measurement of CK and CK-MB activity were drawn every 4 hr for the first 24 hr and every 8 hr for the next 48 hr. Patients received conventional drug therapy with nitrates (n=31), ß-adrenergic blockers (n=17), or calcium antagonists (n=20), alone or in combination according to individual needs, which remained to be the responsibility of the attending physician. The patients with coronary stent implantations also received aspirin and ticlopidine to prevent stent thrombosis. Small number of patients were treated with ACE inhibitors (n=7), digoxin (n=4) or diuretics (n=4) at discharge and during clinical follow-up. Written informed consents were obtained from all included patients and our institutional review board approved the study protocol.

2. Coronary Angiography and Primary Angioplasty

Primary angioplasty was performed according to the standard procedure, and coronary stents were implanted in 29 of 36 patients. Identification of infarct related artery was based on electrocardiographic changes, angiographic appearance of the artery and associated regional wall motion abnormalities on echocardiography. The anterograde flow through the infarct related artery on coronary angiography before and after primary angioplasty was determined using TIMI criteria.[17] Angiographic collateral channels were graded according to Rentrops classification.[18] Routine follow-up coronary angiography to evaluate the patency of infarct related artery was done 7 months after angioplasty in all but 8 patients who refused to undergo coronary angiography.

3. Two-Demensional Echocardiography

All patients underwent echocardiographic examination with HP 2500 (Hewlett Packard Co, Andover, MA, U.S.A.) before the primary angioplasty (baseline), then at 6.7±1.7 days (range 3-10 days), 32.2±8.6 days (range 21-60 days) and 7.5±2.0 months (range 4-12 months) after primary angioplasty. Images were recorded on videotape by a S-VHS cassette recorder for analysis.

Two investigators unaware of the clinical and angiographic data analyzed the echocardiograms, and discrepancies were resolved by consensus. The left ventricular end-systolic and end-diastolic volumes were calculated according to the modified Simpson's rule. Three measurements of the technically best cardiac cycles, avoiding postectopic beats, were taken from each examination and the average volumes were obtained. The volume indexes were obtained by dividing the volume by the body surface area at each time point. The left ventricular ejection fraction (LVEF) was calculated as stroke volume/end-diastolic volume.

Regional wall motion was assessed according to a 16-segment model.[19] For each segment, wall motion was scored as 1 (normal), 2 (hypokinetic), 3 (akinetic) or 4 (dyskinetic). In evaluating regional wall motion abnormality, attention was paid to the systolic thickening in the central portion of each segment. Baseline images were used to assess the initial extent of regional wall motion abnormalities (jeopardized myocardium). A viable, salvaged myocardial segment was defined when there was improved segmental contractile function between baseline and 1 month or 7 months follow-up (a reduction in segmental score of one or more grade).

4. Tl-201 Myocardial Perfusion Imaging

Adenosine stress Tl-201 SPECT was performed at 5.8±2.1 days (3-10 days) after the primary PTCA to evaluate the presence of residual ischemia and the effect of reperfusion therapy. Adenosine was intravenously administered at a rate of 0.14 g/kg/min for 6 min. At 3 min into the adenosine infusion, a dose of 111 MBq of Tl-201 was intravenously injected. Stress myocardial perfusion images were acquired 5 min after the injection with a triple-head gamma camera equipped with general-purpose collimators (TRIAD; Trionix, Twinsburg, OH, U.S.A.), and redistribution images were obtained at 4 hours after the injection. For each acquisition, 90 projections were obtained over 360° with an acquisition time of 25 seconds per projection. The raw SPECT projection images were reconstructed using a Hamming filter with a cut off frequency of 0.7 cycle/cm. No attenuation correction was performed.

The images were visually analyzed in front of a computer console by two independent observers blinded to all clinical information of the patients. Because there were no significant reversible perfusion defects in infarct related territory on stress - redistribution images of all patients, only 4 hour redistribution images were analyzed in the present study. Four hour redistribution tomographic images from the short axis oblique view, long axis horizontal view, and long axis vertical view along with standard polar maps with a "10-band" color palette were shown. Segmental perfusion was scored for each segment using the same 16-segment left ventricular model as that of echocardiography with following criteria : (0=normal, 80-100% of peak myocardial thallium activity; 1 =equivocal, 60-80% of that; 2=moderately decrease, 40-60% of that; 3= severely decrease, 20-40% of that; 4=absent, 0-20% of that).[26]

5. Statistical analysis

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the accuracy of Tl-201 redistribution images for differentiating salvaged from infarcted myocardium.[20] McNemar's chi square test was performed to compare the number of salvaged myocardial segments between 1 and 7-month echocardiographic studies. Numeric data were expressed as mean±s.d., and a p value of less than 0.05 was considered as statistically significant.

Results

The clinical, angiographic and laboratory characteristics of the patients are summarized in Table 1. Twenty-eight patients (78%) underwent follow-up coronary angiography at 8.5±2.2 months (range, 5-13 months) after primary PTCA, which showed restenosis (≥50% stenosis) of infarct related artery in 11 patients (31%). However, there was no total or subtotal occlusion on the follow-up coronary angiography. No patients had cardiac events including recurrent angina, infarction or cardiac death during the clinical follow-up.

LVEF improved significantly after primary PTCA ($p<0.001$). The patients had an average LVEF of 48.7±11.9% at admission, which increased significantly to 50.7±12.2% during the first week ($p<0.002$). LVEF increased thereafter at 7 months (53.8±10.2%, $p<0.05$).

In the baseline echocardiogram, 212 segments within the infarct bed showed abnormal wall motion, 41 being hypokinetic, and 171 akinetic. Wall motion was improved in 78 of the 212 segments on 1 month

Table 1. Baseline clinical, angiographic and laboratory characteristics of 36 patients with acute myocardial infarction who underwent primary PTCA.

Characteristics	Mean ± s.d. or number (%)
Age (year)	57.5 ± 11.9
Sex	
Male	27 (75.0%)
Female	9 (25.0%)
Killip class	
1	15 (41.7%)
2	20 (55.6%)
3	1 (2.8%)
Type of infarct	
Q-wave	31 (86.1%)
Non Q-wave	5 (13.9%)
Peak creatine kinase (U/L)	3811 ± 2494
Peak creatine kinase-MB (ng/mL)	184.9 ± 155.4
Number of diseased coronary vessels*	
1	17 (47.2%)
2	11 (30.6%)
3	8 (22.2%)
Infarct related artery	
Left anterior descending artery	22 (61.1%)
Left circumflex artery	3 (8.3%)
Right coronary artery	11 (30.6%)
Onset to reperfusion (hour)	5.2 ± 2.7
TIMI grade after angioplasty	
2	6 (16.7%)
3	30 (83.3%)
Collateral flow to infarct related artery	
Grade 0	18 (50.0%)
1	13 (36.1%)
2	4 (11.1%)
3	1 (2.8%)

* This is the number of 3 major epicardial coronary arteries having significant stenosis in itself or its branches on coronary angiography. Significant coronary artery disease other than that in the infarct-related artery was defined as ≥50% reduction in luminal diameter of a major epicardial coronary artery or one of its major branches in each of the two orthogonal projections.

follow-up echocardiography and in 97 on 7 months follow-up echocardiography, which were proved to be salvaged myocardium. There was a significant difference in the number of salvaged myocardial segments between 1 and 7-month echocardiographic studies ($p<0.005$).

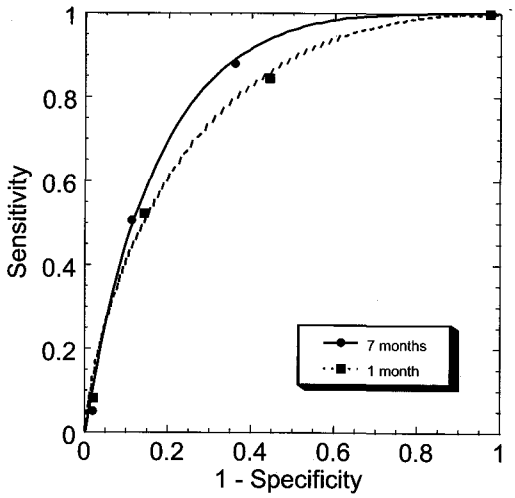

Fig. 1. ROC curves of Tl-201 perfusion score for detecting viable, salvaged myocardium on 1 month and 7 months follow-up.

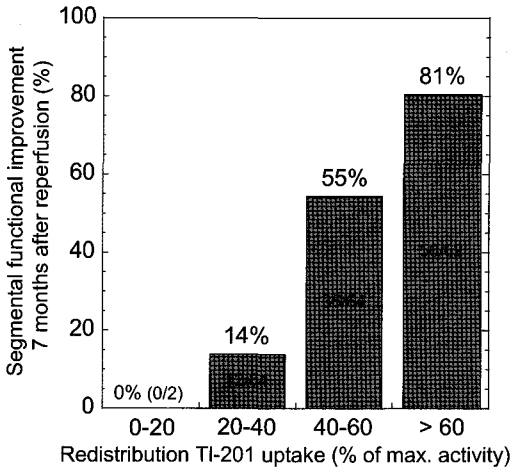

Fig. 2. Linear relationship between the percentage of peak Th-201 activity on early redistribution imaging and the likelihood of segmental functional improvement 7 months after reperfusion.

The area under ROC curves of Tl-201 perfusion score for detecting salvaged segments was 0.79±0.03 for 1 month follow-up and 0.83±0.03 for 7 months follow-up (Fig. 1). Optimum cut-off of perfusion score showing best accuracy was between 2 and 3 (40% of peak thallium activity). Then, sensitivity and specificity of Tl-201 redistribution images for detecting salvaged myocardium is 84.6% (66/78) and 55.2% (74/134) for 1 month follow-up, and 87.6% (85/97) and 64.3% (74/115), respectively. Linear relation between the percentage of peak Th-201 activity on early redistribution imaging and the likelihood of segmental functional improvement 7 months after reperfusion was demonstrated in Fig. 2.

When 171 akinetic segments were included in the analyses, the area under ROC curves of Tl-201 perfusion score for detecting salvaged segments was 0.77±0.04 for 1 month follow-up and 0.83±0.03 for 7 months follow-up. The sensitivity and specificity of Tl-201 redistribution images for detecting salvaged myocardium was 76.9% (40/52) and 58.8% (70/119) for 1 month follow-up, and 82.1% (55/67) and 68.3% (71/104), respectively.

Discussion

In experimental models of reperfusion, Tl-201 may underestimate infarct size immediately after coronary reperfusion possible due to coronary hyperemia,[21,22] but this underestimation appears to resolve by 48 hours.[23] If the extent of regional wall motion abnormalities on baseline echocardiography can be assumed to reflect the extent of jeopardizing myocardium and the residual perfusion defect on the Tl-201 SPECT images obtained more than 3 days later after reperfusion can be considered an estimate of infarcted myocardial tissue, then the difference between the segments with regional wall motion abnormalities on baseline echocardiography and the segments with residual perfusion defect is the scintigraphic expression of the amount of salvaged myocardium.

In this study, early Tl-201 redistribution images performed at 6.5 days after primary PTCA showed

good results for differentiating salvaged and infarcted myocardium as defined by early (area under ROC curve for 1 month follow-up=0.79) and late (area under ROC curve for 7 month follow-up=0.83) functional recovery. Linear relation between the percentage of peak thallium activity on early redistribution imaging and the likelihood of segmental improvement 7 months after reperfusion was found in the present study. This suggests that many mild to moderate fixed thallium defects shown early after reperfusion do not reflect myocardial scar but remain salvaged or stunned myocardium, and will show functional recovery. The similar linear relation was also observed in rest Tl-201 imaging study for viability assessment in patients with chronic coronary artery disease.[24,25] In this study, 40% of peak myocardial thallium activity could differentiate salvaged from infarcted segment 7 months after reperfusion with best accuracy. This was comparable to 45% threshold of previous experimental pathological and clinical studies.[26,27] For Tc-99m sestamibi, however, it is well known that 60% of peak myocardial activity is best cutoff for differentiating viable from infarcted myocardium which was proven by phantom, clinical and pathological studies.[28-30] This resulted in larger estimate of infarct size measured by thallium than that by sestamibi in the same threshold.[27,28]

Tl-201 perfusion imaging before reperfusion therapy is not suitable in patients with acute MI for assessing the entity of jeopardized myocardium or the achievement of reperfusion after reperfusion therapy, because of rapid redistribution of Tl-201 : it needs at least 20-30 minutes to organize and perform initial study. Such a technically mandatory delay in the begining of reperfusion therapy is absolutely not feasible for the prognosis of patients. Tc-99m sestamibi practically does not redistribute after initial cardiac uptake : it can be injected just before reperfusion therapy, and imaging can be acquired an hour or even later when therapy administration is over and the patient is in more stable conditions.[13,14] However, it still needs a 20-30 minutes preparation and should be injected within 6-8 hours, given the absence of any bacteriostatic. Furthermore, emergent preparation of radiopharmaceutical kit and performance of imaging, especially in the nighttime or holidays are not available in all institutes. Therefore, it is desirable if early single myocardial perfusion imaging after reperfusion therapy can differentiate salvaged or stunned myocardium from infarcted myocardium in such patients. In the present study, Tl-201 redistribution imaging performed at 6.5 days after reperfusion therapy could predict wall motion recovery up to 7 months after infarction with high sensitivity of 87.6%.

There were controversies in the indication of Tl-201 myocardial perfusion imaging performed early within 2-4 weeks after reperfusion in patients with acute MI because of high false positive rate of restenosis.[31] However, this study demonstrated that single Tl-201 myocardial perfusion imaging performed early within 10 days after reperfusion was useful to predict the wall motion recovery up to 7 months in patients with acute MI.

This study had several limitations. The small patient population is the first major limitation of this study. Secondly, regional perfusion on Tl-201 SPECT images was compared with regional wall motion on echocardiography using 16-segment model. Because of inherent difference in the orientation of 2-dimensional image in echocariography and 3-dimensional tomographic Tl-201 images for examining heart, it is possible that there may be some misalignment between the same segments designated by echocardiography and Tl-201 images. Thirdly, we did not perform Tl-201 reinjection or 24 hr redistribution imaging studies. However, the benefit of obtaining additional

reinjection or 24 hour redistribution studies has not been completely validated in patients with acute myocardial infarction[32,33]

Conclusion

Tl-201 myocardial perfusion SPECT imaging performed early within 10 days after reperfusion can be used to predict the salvaged myocardium and functional recovery with high sensitivity during the 7 months following primary PTCA in patients with acute MI.

Summary

Purpose : The amount of salvaged myocardium is an important prognostic factor in patients with acute myocardial infarction (MI). We investigated if early Tl-201 SPECT imaging could be used to predict the salvaged myocardium and functional recovery in acute MI after primary PTCA. **Materials and Methods :** In 36 patients with first acute MI treated with primary PTCA, serial echocardiography and Tl-201 SPECT imaging (5.8±2.1 days after PTCA) were performed. Regional wall motion and perfusion were quantified with on 16-segment myocardial model with 5-point and 4-point scaling system, respectively. **Results :** Wall motion was improved in 78 of the 212 dyssynergic segments on 1 month follow-up echocardiography and 97 on 7 months follow-up echocardiography, which were proved to be salvaged myocardium. The areas under receiver operating characteristic curves of Tl-201 perfusion score for detecting salvaged myocardial segments were 0.79 for 1 month follow-up and 0.83 for 7 months follow-up. The sensitivity and specificity of Tl-201 redistribution images with optimum cutoff of 40% of peak thallium activity for detecting salvaged myocardium were 84.6% and 55.2% for 1 month follow-up, and 87.6% and 64.3% for 7 months follow-up, respectively. There was a linear relationship between the percentage of peak thallium activity on early redistribution imaging and the likelihood of segmental functional improvement 7 months after reperfusion. **Conclusion :** Tl-201 myocardial perfusion SPECT imaging performed early within 10 days after reperfusion can be used to predict the salvaged myocardium and functional recovery with high sensitivity during the 7 months following primary PTCA in patients with acute MI.

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