

## Early Prediction of Myocardial Salvage After Primary Coronary Angioplasty: Comparative Study of Coronary Flow Velocity Pattern Immediately After Primary Coronary Angioplasty and Perfusion-Metabolism Mismatch

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### Abstract

**Objectives.** Perfusion-metabolism mismatch in the subacute phase using thallium-201/radio iodinated beta-methyl-*p*-iodophenyl pentadecanoic acid (TI/BMIPP) dual scintigraphy is an indicator of viable myocardium in acute myocardial infarction. This study investigated early prediction of myocardial salvage from the TI/BMIPP mismatch and coronary flow velocity (CFV) patterns in patients with acute myocardial infarction.

**Methods.** Thirty three patients with first anterior wall myocardial infarction underwent primary coronary angioplasty and achieved reflow within 8 hr of onset. By using a Doppler guide wire, CFV patterns were assessed immediately after primary coronary angioplasty. TI/BMIPP dual scintigraphy was performed within 3 days after reperfusion. The extent of discordance in severity score was defined as the TI/BMIPP mismatch score.

**Results.** Regression analysis showed dual scintigraphy mismatch score correlated well with deceleration time of diastolic flow velocity ( $r = 0.54, p < 0.01$ ). Mismatch score was greater in the non-early systolic reversal flow group than in the early systolic reversal flow group ( $5.5 \pm 3.3$  vs  $1.9 \pm 2.1$ , respectively,  $p < 0.01$ ).

**Conclusions.** Changes in CFV patterns correlated well with TI/BMIPP mismatch score. CFV pattern immediately after reperfusion is useful for early prediction of myocardial salvage.

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Reperfusion

Prognosis

**INTRODUCTION**

Early recanalization through the use of angioplasty is established as an essential therapy for acute myocardial infarction (AMI). However, despite successful recanalization by primary percutaneous coronary intervention (PCI), a substantial number of patients still fail to obtain complete and sustained myocardial reperfusion and remain at risk of developing large infarcts. The failure to achieve adequate tissue perfusion is referred to as the no-reflow phenomenon, which occurs as a result of microvascular damage or intramyocardial edema induced by ischemia.<sup>1-5)</sup> Assessment of myocardial viability is important to predict functional recovery and future cardiac events with AMI.

The intracoronary Doppler guide wire facilitates the measurement of the coronary flow velocity distal to coronary lesions immediately after angioplasty to AMI patients. The coronary flow velocity (CFV) pattern is predictive of the recovery of global left ventricular function and in-hospital survival in patients with AMI.<sup>6-11)</sup> Nuclear imaging techniques with the use of the radiolabelled fatty acid analogue iodine-123 beta-methyl-*p*-iodophenyl pentadecanoic acid (<sup>123</sup>I-BMIPP) have demonstrated reduced fatty acid uptake and increased glucose uptake in response to less fatty acid utilization in dysfunctional but viable myocardium. Ischemic "memory image" is a phenomenon of <sup>123</sup>I-BMIPP in which areas at risk of AMI could be detected as a defect within a couple of weeks even after successful reperfusion.<sup>12,13)</sup> Perfusion-metabolism mismatch using <sup>201</sup>Tl/<sup>123</sup>I-BMIPP dual single photon emission computed tomography (SPECT) indicate myocardial salvage in patients with reperfused AMI.<sup>14-16)</sup>

This study examined the relationship between the distal coronary flow dynamics of culprit vessels immediately after successful PCI and perfusion-metabolism mismatch detected by <sup>201</sup>Tl/<sup>123</sup>I-BMIPP dual SPECT in patients with reperfused anterior-wall AMI.

**SUBJECTS AND METHODS****Study patients**

The study prospectively enrolled 35 consecutive

patients who underwent successful primary coronary stenting in the proximal or the mid portion of the left anterior descending coronary artery (LAD) after the diagnosis of first anterior AMI between January 1999 and March 2003. The infarction was confirmed by chest pain of > 30 min duration, pathologic Q waves, > 2 mV ST elevation in at least 2 contiguous electrocardiographic leads, and greater than three-fold increase in serum creatinine kinase levels. Only patients with total occlusion [*i.e.* Thrombolysis in Myocardial Infarction (TIMI) grade 0 or 1 flow] in the proximal or in the mid portion of LAD were included. All patients had received intervening revascularization procedures at the time of hospital admission. Two patients were excluded from analysis because of inadequate image quality of Doppler signals. Therefore, only 33 patients (mean age 64 years, 29 men and 4 women) were included, who also had satisfactory opening of culprit lesion as evaluated angiographically at the time of discharge. Informed consent was obtained from each patient.

**Coronary intervention**

After the diagnostic angiography, PCI was performed in the usual manner with 8F or 7F guiding catheters. Each patient received 200 mg aspirin and heparin (100 IU/kg intravenous) before PCI. The final end point of coronary intervention was defined as a residual stenosis < 30% (determined by angiography), with TIMI 3 flow. All patients received ticlopidine (200 mg twice a day) and aspirin (200 mg), whereas nonstented patients were given aspirin (100 mg) only. Each patient underwent predischARGE coronary angiography.

**Resting <sup>201</sup>Tl/<sup>123</sup>I-BMIPP dual SPECT analysis**

After overnight fasting, each patient received an intravenous injection of <sup>123</sup>I-BMIPP (111 MBq), and <sup>201</sup>Tl (111 MBq) within 3 days after reperfusion. Initial images were obtained 20 min after the injection, and delayed images were obtained 4 hr later. <sup>201</sup>Tl/<sup>123</sup>I-BMIPP SPECT used a single head gamma scintillation camera equipped with a low energy, all purpose parallel whole collimator. The 150 - 160 keV photo peaks for <sup>123</sup>I and the 70 - 80 keV photo peaks for <sup>201</sup>Tl with 10 - 20% window were selected

for dual-isotope data acquisitions. A filtered back-projection algorithm was used for reconstructing short-axis and horizontal long-axis tomograms. The SPECT images were analyzed individually by two experienced observers unaware of the patients' clinical data. Disagreements in interpretation were resolved by consensus of the two observers. A composite of the left ventricle was created by computerized techniques and divided into 20 segments.<sup>17)</sup>  $^{123}\text{I}$ -BMIPP and  $^{201}\text{Tl}$  defect in each segment were scored semi-quantitatively using a 4 point grading system (0 = normal, 1 = mildly reduced uptake, 2 = highly reduced uptake, 3 = absent activity). Abnormal uptakes of  $^{201}\text{Tl}$  and  $^{123}\text{I}$ -BMIPP were shown as total defect scores by the summation of each score in 20 left ventricular segments. The mismatch score of  $^{201}\text{Tl}$  and  $^{123}\text{I}$ -BMIPP was calculated using the following formula: mismatch score = ( $^{123}\text{I}$ -BMIPP score minus  $^{201}\text{Tl}$  score in each segment).<sup>16)</sup>

### Quantitative coronary angiographies

Coronary angiography and coronary angioplasty were performed with standard catheters using non-ionic, low-osmolarity contrast agents. No drugs with potentially rheological capacities (e.g.  $\beta$  or  $\alpha$  receptor blockers or adenosine) were used in any patient. Arterial diameter at angioplasty site was measured on end-diastolic frames. Coronary angiography was performed using the Philips DCI system. Coronary angiographic data were quantitatively analyzed offline by auto edge detection with a validated technique (CMS; Medical Imaging Systems, Inc)<sup>18)</sup> from a cineangiogram taken before and after primary PCI. The contrast flow through the infarct-related coronary artery was graded by the TIMI flow classification.<sup>19)</sup> Collateral flow was graded according to the Rentrop classification of 0 to 3 from the initial coronary angiogram.<sup>20)</sup> Cine film was analyzed by an angiographer unaware of patient data.

### Intracoronary Doppler flow measurements

After completion of the interventional recanalization, the guide wire was exchanged for a 0.014-in intracoronary Doppler-tipped flow wire (12 MHz, FloWire, Volcano Inc) to perform intracoronary flow measurements. The tip of the wire was advanced across the culprit lesion and placed at least 3 to 4 cm distal to the lesion. Doppler flow velocity spectra were analyzed online to determine

time-averaged peak flow velocity. CFV was continuously measured until 20 min after the end of stenting. Doppler measurements were repeated 2 times and recorded on super VHS videotape. Doppler-derived flow volume was calculated as described before.<sup>21)</sup> The digitized coronary blood flow velocity spectrum provided the following parameters: time-averaged peak velocity (cm/sec), systolic peak velocity (cm/sec), and diastolic peak velocity (cm/sec), deceleration time of diastolic flow (msec), averaged systolic-time velocity integral, and early systolic reverse flow (ESRF).

### Statistical analysis

Continuous variables are presented as mean  $\pm$  SD. Comparisons between two groups were made with the unpaired *t*-test. A one-way analysis of variance with a Fisher's protected least significant difference test was used to compare variables between patient groups. To gain insight into the effect of creatine kinase, and elapsed time from the onset of symptoms until reperfusion on  $^{201}\text{Tl}/^{123}\text{I}$ -BMIPP mismatch, analysis of covariance (ANCOVA) was performed using peak creatine kinase and elapsed time as covariates. Simple linear regression was performed to examine the relationship between coronary flow velocity variables and  $^{201}\text{Tl}/^{123}\text{I}$ -BMIPP mismatch.  $p < 0.05$  was considered statistically significant.

## RESULTS

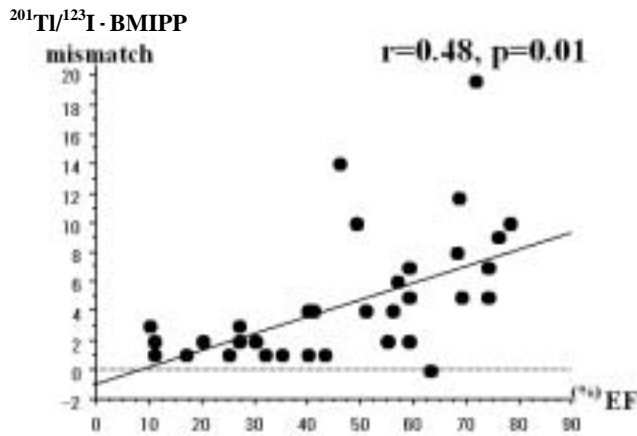
### Patient characteristics and clinical results

Baseline clinical characteristics and hemodynamic data are shown in **Table 1**. Eleven patients (33%) had a history of hypertension, 9 (27%) had diabetes mellitus and 12 (36%) had total cholesterol level  $> 220$  mg/dl or received lipid lowering therapy. Nineteen patients (58%) were smokers. Mean time from the onset of symptoms to coronary reperfusion was  $4.5 \pm 2.2$  hr. Peak creatine kinase level was  $4,215 \pm 2,497$  IU/l. Twenty-nine patients developed Q-wave infarction, whereas the other 4 manifested non-Q-wave infarction. There was no clinical, electrocardiographic, or enzymatic evidence of reinfarction in any patient during the 1-month follow-up. In-hospital medications were as follows: nitrate ( $n = 32$ ; 97%), angiotensin converting enzyme inhibitor ( $n = 30$ ; 91%), adrenergic blocking agent ( $n = 1$ ; 3%), calcium antagonist ( $n = 5$ ; 15%), and diuretics ( $n = 5$ ; 15%).

**Table 1 Clinical characteristics of study population**

Number of patients	33
Sex( male/female )	29/4
Age( yr )	64 ± 9
Coronary risk factors	
Hypertension	11( 33 )
Diabetes mellitus	9( 27 )
Hyperlipidemia	12( 36 )
Smoking	19( 58 )
Pre-infarction angina( < 24 hr )	17( 52 )
Results of recanalization	
Peak creatine kinase( IU/l )	4,215 ± 2,497
Time to recanalization( hr )	4.5 ± 2.2
Left ventricular ejection fraction( after 1 month )( % )	59 ± 12
Coronary angiographic findings	
Segment 6/segment 7	23/10
Number of diseased vessels	1.4 ± 0.6
Reference diameter( mm )	3.1 ± 1.0
Minimum lumen diameter( mm )	0.3 ± 0.2
Intraaortic balloon pumping	9( 6 )

Continuous values are mean ± SD. ( ) %.

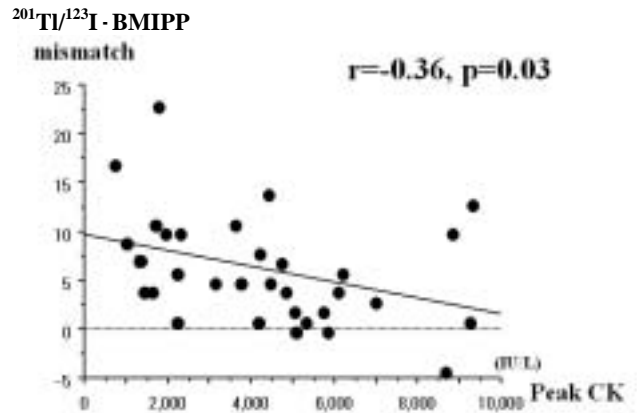


**Fig. 1** Linear regression analysis showing  $^{201}\text{Tl}/^{123}\text{I}$ -BMIPP mismatch score correlated with global left ventricular ejection fraction at 1 month

Tl = thallium; I = iodine; BMIPP = beta-methyl-p-iodophenyl pentadecanoic acid; EF = ejection fraction.

### Angiographic results

Primary PCI was successfully performed in all patients. The culprit lesions were located in the proximal LAD in 23 patients and mid LAD in 10 patients. Twenty-nine patients had single-vessel disease, and 4 had double-vessel disease. No patient showed good collateral flow( Rentrop grade



**Fig. 2** Linear regression analysis showed the  $^{201}\text{Tl}/^{123}\text{I}$ -BMIPP mismatch score correlated with peak creatine kinase

CK = creatine kinase. Other abbreviations as in Fig. 1.

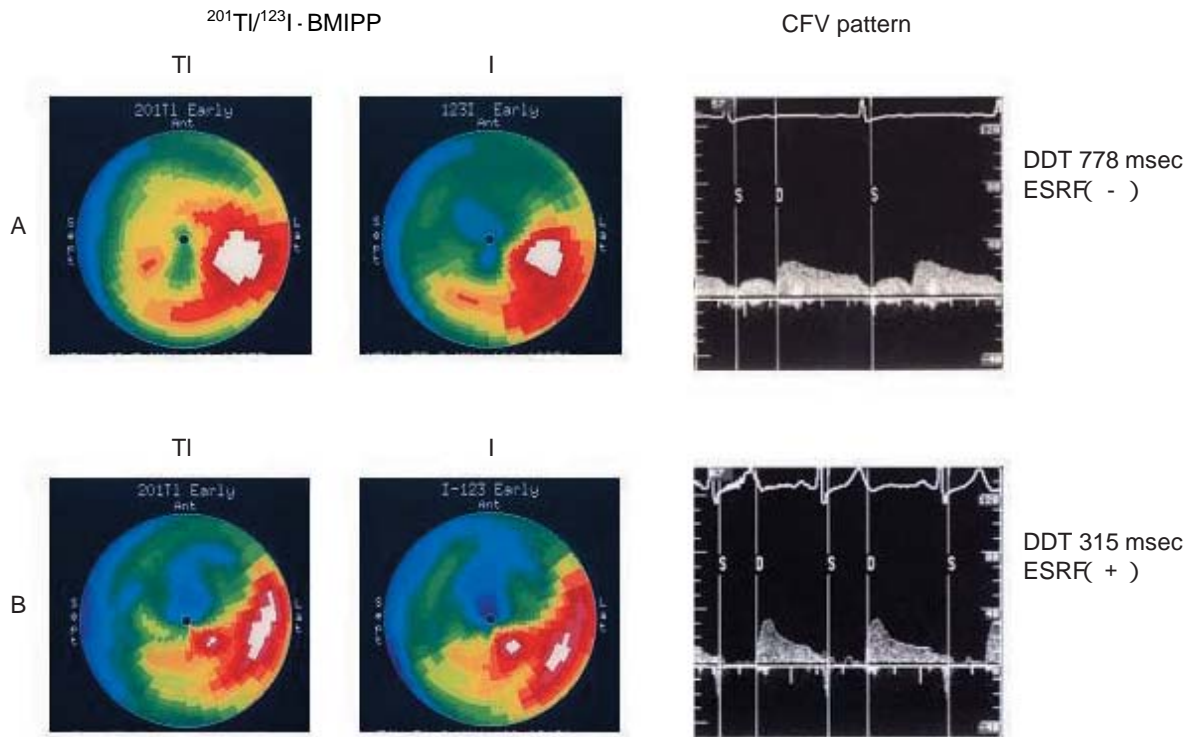
3), two showed fair collateral flow( Rentrop grade 2) and the remaining 31 showed poor or no collateral flow( Rentrop grade 1 or 0) on the initial coronary angiogram. Initial coronary angiography showed TIMI grades 0, 1, 2 and 3 in 30, 3, 0 and 0 cases, respectively. Percentage diameters of stenosis before and after angioplasty were  $95 \pm 15\%$  and  $26 \pm 15\%$ , respectively. Minimum lumen diameter after angioplasty was  $2.4 \pm 0.7\text{ mm}$ . All patients showed TIMI 3 reflow. No patient had insignificant stenosis distal to the culprit lesion.

### $^{201}\text{Tl}/^{123}\text{I}$ -BMIPP mismatch and left ventricular function

Linear regression analysis showed the  $^{201}\text{Tl}/^{123}\text{I}$ -BMIPP mismatch score was predictive of the recovery of global left ventricular function at 1 month(  $r = 0.48, p = 0.01$ ; **Fig. 1** ). The mismatch score was correlated with peak creatine kinase after reperfusion(  $r = -0.36, p = 0.03$ ; **Fig. 2** ). The perfusion-metabolism mismatch evaluated by the  $^{201}\text{Tl}/^{123}\text{I}$ -BMIPP dual SPECT indicated myocardial salvage in patients with reperfused AMI.

### Coronary flow velocity variables and $^{201}\text{Tl}/^{123}\text{I}$ -BMIPP mismatch

Two representative examples of the post angioplasty phasic velocity profiles and  $^{201}\text{Tl}/^{123}\text{I}$ -BMIPP SPECT images are shown in **Fig. 3**. There were significant differences between these two patients in the CFV patterns. **Fig. 3 - A** shows a good reflow and mismatched patient.  $^{201}\text{Tl}/^{123}\text{I}$ -BMIPP uptakes were mismatched. CFV pattern immediately after



**Fig. 3** Representative examples of post angioplasty phasic velocity profiles and <sup>201</sup>Tl/<sup>123</sup>I-BMIPP images

**A:** Mismatch with <sup>201</sup>Tl/<sup>123</sup>I-BMIPP uptakes. Coronary flow velocity pattern immediately after reperfusion shows good reflow pattern as slow deceleration time of diastolic flow, no early systolic reversal flow, and normal systolic antegrade flow.

**B:** No mismatch or broad perfusion defect. Coronary flow velocity pattern shows no reflow pattern as rapid deceleration time of diastolic flow, early systolic reversal flow, and diminished systolic antegrade flow.

CFV = coronary flow velocity; DDT = deceleration time of diastolic flow; ESRF = early systolic reversal flow. Other abbreviations as in Fig. 1.

**Table 2** Phasic coronary flow velocity patterns immediately after reperfusion

Heart rate( beats/min )	71 ± 14
Time-averaged peak velocity( cm/sec )	20 ± 6.4
Systolic peak velocity( cm/sec )	5.4 ± 10
Diastolic peak velocity( cm/sec )	27 ± 13
Diastolic systolic velocity ratio	5.5 ± 8.3
Deceleration time of diastolic flow( msec )	605 ± 68
Early systolic reverse flow	1 ( 37% )

Continuous values are mean ± SD.

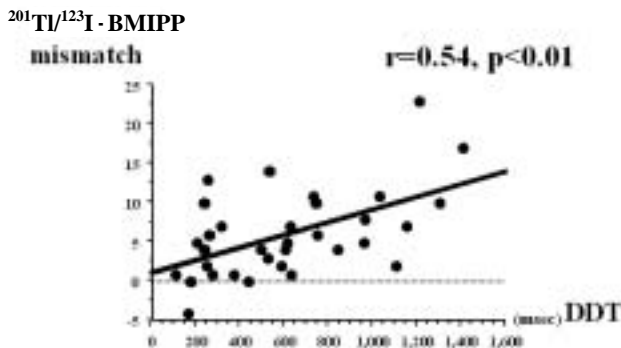
reperfusion showed good reflow pattern as slow deceleration of diastolic flow, no ESRF, and normal systolic antegrade flow. **Fig. 3 - B** shows a no-reflow and matched patient. <sup>201</sup>Tl/<sup>123</sup>I-BMIPP SPECT showed no mismatch or broad perfusion defect. CFV pattern showed no reflow pattern as rapid deceleration of diastolic flow, ESRF and

diminished systolic antegrade flow.

After completion of the interventional recanalization, intracoronary flow measurements were performed. Flow velocity variables at steady state after PCI are shown in **Table 2**. We analyzed correlations between CFV variables and the perfusion-metabolism mismatch score detected by <sup>201</sup>Tl/<sup>123</sup>I-BMIPP dual SPECT. Linear regression analysis showed <sup>201</sup>Tl/<sup>123</sup>I-BMIPP mismatch score correlated well with deceleration time of diastolic flow velocity(  $r = 0.54, p < 0.01$ ; **Fig. 4** ) time-averaged peak velocity(  $r = 0.39, p = 0.02$  ), and averaged systolic-time velocity integra(  $r = 0.47, p = 0.005$  ). <sup>201</sup>Tl/<sup>123</sup>I-BMIPP mismatch score was significantly greater in the non-ESRF group than in the ESRF group(  $5.5 ± 3.3$  vs  $1.9 ± 2.1$ , respectively,  $p < 0.01$ ; **Fig. 5** )

## DISCUSSION

Our study demonstrated that CFV patterns were



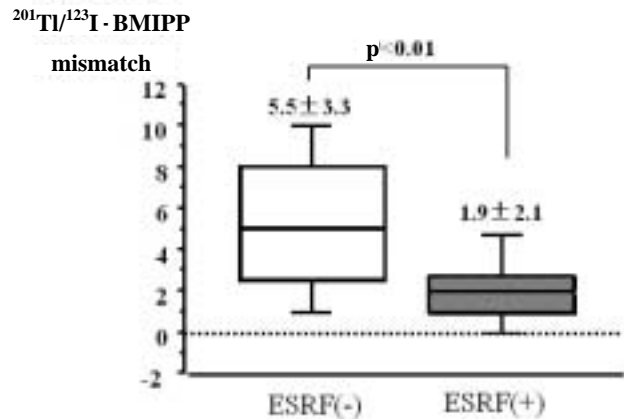
**Fig. 4** Linear regression analysis showing  $^{201}\text{Tl}/^{123}\text{I}$ -BMIPP mismatch score correlated with deceleration time of diastolic flow velocity  
Abbreviations as in Figs. 1, 3.

associated with perfusion-metabolism mismatch detected by  $^{201}\text{Tl}/^{123}\text{I}$ -BMIPP dual SPECT. These observations indicate that the good re-flow detected from the CFV pattern is useful for predicting myocardial salvage and functional recovery of postischemic myocardium.

In our patients, the  $^{201}\text{Tl}/^{123}\text{I}$ -BMIPP mismatch score was predictive of the recovery of global left ventricular function and peak creatine kinase after reperfusion. The perfusion-metabolism mismatch evaluated by  $^{201}\text{Tl}/^{123}\text{I}$ -BMIPP dual SPECT indicated myocardial salvage in patients with reperfused AMI.

$^{123}\text{I}$ -BMIPP is a radioiodinated fatty acid analogue, into which a methyl group has been introduced in the -3 position of the fatty acid chain to inhibit rapid myocardial catabolism. Therefore,  $^{123}\text{I}$ -BMIPP has a long retention time in the myocardium because of its incorporation into the triglyceride pool.<sup>12,13</sup> Myocardial BMIPP activity is proportional to the intracellular adenosine triphosphate level, and reduced myocardial activity of BMIPP is a sensitive indicator of ischemic injury in both viable and infarcted myocardium. Clinical protocols using BMIPP have been performed at several institutions for the evaluation of the impairment of myocardial fatty acid metabolism and of myocardial viability.<sup>14-16</sup> This study evaluated the myocardial perfusion by thallium imaging and the myocardial fatty acid metabolism by BMIPP imaging.

Tomographic BMIPP imaging in the subacute phase provides the amount of myocardium at risk after AMI.<sup>22</sup> The ability of BMIPP imaging at 1 week post AMI to identify areas at risk is similar to that of tetrofosmin perfusion imaging in the acute



**Fig. 5**  $^{201}\text{Tl}/^{123}\text{I}$ -BMIPP mismatch score showing a significant increase in the non-ESRF group compared to the ESRF group  
Abbreviations as in Figs. 1, 3.

phase. This may be due to the impairment of fatty acid uptake and metabolism reflecting prior severe ischemic insult which persists at least 1 week after recovery of perfusion in the acute phase of AMI. We used a semiquantitative method to assess how perfusion-metabolism mismatch contributes to determining the extent of surviving and infarcted myocardium at an infarct-related zone. We performed dual scintigraphy within 3 days after reperfusion to assess the area at risk. The presence of a large amount of perfusion-metabolism mismatch as evaluated by  $^{201}\text{Tl}/^{123}\text{I}$ -BMIPP dual SPECT can identify patients with the best prognosis.<sup>23</sup>

Intracoronary myocardial contrast echocardiography studies have shown that up to 30% of patients undergoing primary angioplasty lack myocardial reperfusion despite recanalization of the infarct-related artery.<sup>1-4</sup> These regions of "no-reflow" may develop because of microvascular disruption, plugging by thromboembolic debris, or endothelial and myocardial edema. New aspects of the phasic Doppler waveform, namely prolonged diastolic deceleration with a positive diastolic/systolic average peak velocity ratio, translate into functional myocardial recovery after stenting despite the presence of an abnormal coronary flow reserve.<sup>10</sup> In addition, rapid diastolic deceleration with a significant systolic flow reversal pattern before or after coronary intervention indicates that the microcirculatory abnormalities must have been extensive and prohibitive regarding functional recovery. These novel flow patterns are an accurate predictor of the complications and in-hospital survival after AMI.<sup>11</sup>

The association of the perfusion-metabolism mismatch detected by the  $^{201}\text{Tl}/^{123}\text{I}$ -BMIPP dual SPECT and the CFV patterns has not been clarified. The metabolic impairment in viable myocardium may be elucidated by the CFV patterns.

The present study showed close correlation of the extent of perfusion-metabolism mismatch with the CFV patterns. These findings strongly suggest that CFV patterns can estimate augment perfusion-metabolism mismatch related to transient wall motion abnormality and fatty acid metabolism by salvaging myocardium in the area at risk. Catheter-based measurements of microvascular function promise to further improve the outcome of AMI patients.

This study has several limitations. First, the number of patients is relatively small and were observed only in the acute phase. The results from 33 consecutive AMI patients strongly suggest the need for a larger patient population and longer follow-up

period. Second, the timing of SPECT after coronary reflow is a factor affecting the size of the risk area. Third, only patients with first anterior AMI were enrolled in this study. Therefore, the prognostic value of CFV pattern has not been established in patients with inferior or posterior wall AMI or recurrent myocardial infarction. Finally, our analysis was based on in-hospital complications and angiographic data only. Determination of survival and quality of life needs a longer follow-up period.

## CONCLUSIONS

The present study demonstrated that the CFV pattern is associated with perfusion-metabolism mismatch detected by  $^{201}\text{Tl}/^{123}\text{I}$ -BMIPP dual SPECT. The present study clarified the CVF pattern indicative of viable myocardium. High risk patients can be detected by Doppler flowmetry during an earlier stage of AMI.

## 要 約

再灌流療法後の救済心筋の早期予測: 冠動脈血流速波形と血流-代謝ミスマッチとの比較

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目 的: 急性心筋梗塞後の亜急性期に施行した $^{201}\text{Tl}$ と $^{123}\text{I}$ -BMIPPの2核種同時撮像のシンチグラフィによる血流と代謝のミスマッチ領域は、再灌流療法により救済された心筋を示している。急性心筋梗塞患者に対する再灌流療法後の救済心筋の早期評価の指標として、本法のミスマッチと再灌流直後の冠動脈血流速波形との相関について検討した。

方 法: 発症8時間以内に再灌流療法を行った初回前壁中隔梗塞患者33例を対象とした。冠動脈血流速波形は再灌流後に冠動脈内ドップラーワイヤーにより測定し、no reflowの指標となる拡張期減衰時間や収縮早期逆流波の有無などにつき計測した。2核種同時撮像のシンチグラフィは再灌流後3日以内に行った。ミスマッチは、それぞれの集積を半定量的に評価し、それぞれのスコアの差をミスマッチスコアとした。

結 果: 回帰分析では、シンチグラフィによるミスマッチスコアは冠血流速波形の拡張期減衰時間と相関した( $r = 0.54, p < 0.01$ )。また、ミスマッチスコアは収縮早期逆流波を認めない群で有意に高かった( $5.5 \pm 3.3$  vs  $1.9 \pm 2.1, p < 0.01$ )

結 論: 再灌流後の冠血流速波形と $\text{Tl}/\text{BMIPP}$ ミスマッチスコアには有意な相関を認めた。再灌流後の冠血流速波形は救済心筋の早期評価の指標として有用である。

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