Detecting Viable Myocardium and Predicting Functional Improvement

Comparisons of Positron Emission Tomography, Rest-Redistribution Thallium-201 Single-Photon Emission Computed Tomography (SPECT), Exercise Thallium-201 Reinjection SPECT, I-123 BMIPP SPECT and Dobutamine Stress Echocardiography

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Background

Low-dose dobutamine stress echocardiography (LDDE) has become a useful and safe method for identifying hibernating or stunned myocardium and for predicting improvement in wall motion after coronary revascularization.

Methods and Results

In the present study, fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET), rest-redistribution thallium-201 (201Tl) single-photon emission computed tomography (RR-Tl SPECT), 123I-15-(p-iodophenyl)-3-(R,S)-methyl pentadecanoic acid (BMIPP) and LDDE were performed in 30 patients with acute myocardial infarction (AMI) at 10±3 days after the onset of AMI. Also, exercise 201Tl reinjection SPECT (RI-Tl SPECT) was performed at 14±2 days. Follow-up echocardiography was performed 5±3 months later in all patients after interventional therapy for the assessment of functional recovery. Of the 390 segments analyzed by echocardiography, 110 (28%) had abnormal wall motion. There were no significant differences between RR-Tl SPECT and LDDE in sensitivity, specificity, positive predictive value and negative predictive value using the \( \chi^2 \)-test; however, in akinetic segments, there was a significant difference in sensitivity. Among FDG-PET, RI-Tl SPECT, BMIPP and LDDE, there were significant differences in 3 variables. In akinetic segments, LDDE is superior to RR-Tl SPECT in sensitivity and to FDG-PET in specificity. In hypokinetic segments, LDDE is superior to RI-Tl SPECT and BMIPP in sensitivity, and to FDG-PET and BMIPP in specificity.

Conclusions

LDDE could detect functional recovery of viable myocardium in the early period of AMI and can be performed easily and safely. (Circ J 2004; 68: 950–957)

Key Words: BMIPP; FDG-PET; LDDE; Myocardial viability; Tl-SPECT

The detection of viable myocardium in patients with acute myocardial infarction (AMI) is important for predicting functional recovery. Several imaging techniques have been used to detect myocardial viability. Rest-redistribution thallium-201 (201Tl) single-photon emission computed tomography (RR-Tl SPECT) \(^1\)–\(^3\) and exercise 201Tl reinjection SPECT (RI-Tl SPECT) \(^4\)–\(^5\) have been proposed as effective methods for the evaluation of myocardial viability. Fluorine-18 (18F) fluorodeoxyglucose positron emission tomography (FDG-PET), which assesses the myocardial uptake of 18F fluorodeoxyglucose, reflects myocardial metabolic activity and has been the gold standard for detecting viable myocardium.\(^8\)–\(^12\) However, metabolic SPECT imaging with 123I-15-(p-iodophenyl)-3-(R,S)-methyl pentadecanoic acid (BMIPP), an iodinated fatty acid analogue, can be used to predict the reversibility of dysfunctional segments after coronary artery revascularization in patients with a previous myocardial infarction (MI).\(^13\),\(^14\)

The clinical usefulness of BMIPP imaging in patients with AMI has been recently reported.\(^15\),\(^16\) Naruse et al reported that BMIPP images in the infarct region showed a higher correlation with wall motion abnormalities by echocardiography in the acute phase and that delayed 201Tl images showed the highest correlation with wall motion abnormalities in the chronic phase.\(^16\) Dobutamine stress echocardiography (DSE) has become a useful and safe method for identifying hibernating or stunned myocardium in order to predict improvement in wall motion after coronary revascularization in patients with coronary artery disease.\(^17\)–\(^19\) Some previous studies compared 201Tl-SPECT with DSE for assessment of myocardial viability \(^3\)–\(^7\) and we have compared low-dose dobut-

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amine stress echocardiography (LDDE) with FDF-PET for predicting functional recovery in patients with myocardial infarction after revascularization. Yasugi et al reported that combined assessment by dual SPECT (201Tl and 123I BMIPP) and DSE may be useful for detecting myocardial viability and jeopardized myocardium. However, none have compared all 5 methods (FDG-PET, RR-Tl SPECT, RI-Tl SPECT, BMIPP and LDDE) for detecting myocardial viability in an individual patient.

Our aim was to compare the ability of these 5 methods to detect viability as a means of predicting functional recovery assessed by follow-up echocardiography.

Methods

Patient Population

We studied 30 patients (29 men, 1 woman; mean age 62±11 years) with AMI. The site of infarction was the anterior wall in 16 patients and the inferior wall in 14 patients. All patients had Q wave infarcts on electrocardiography (ECG) and regional wall motion abnormalities according to rest echocardiography. There were no patients who had obvious diabetic status. All patients underwent primary percutaneous transluminal coronary angioplasty (PTCA) within 24 h of the onset of MI. All patients were clinically stable during the entire study protocol and none suffered from post-infarction angina or other complications. All patients underwent FDG-PET, RR-Tl SPECT, BMIPP and LDDE during the same period. We performed FDG-PET, RR-Tl SPECT, BMIPP and LDDE in patients with AMI at 10±3 days after the onset of AMI. RI-Tl SPECT was performed at 14±2 days. Follow-up echocardiography was performed 5±3 months after interventional therapy in all patients for the assessment of functional recovery. At the follow-up, we also studied coronary angiography. There were no patients with restenosis or reocclusion of the culprit vessel at follow-up.

All patients gave written informed consent.

Resting BMIPP and 201Tl Dual Isotope SPECT

After overnight fasting, each patient received an intravenous injection of BMIPP (111 MBq) and 201Tl (111 MBq) at rest. Initial images were obtained 20 min after the injection, and delayed images were obtained 4 h later (Fig 1). SPECT was performed using a single-head scintillation camera equipped with a low energy, parallel hole collimator. Thirty-two equidistant projections were acquired over 180° from the right anterior oblique to the left posterior oblique. These images from the 2 energy windows (159 keV±3.5% for iodine-123 and 70 keV±10% for 201Tl) were collected in separate 64×64 matrices and then reconstructed using the Butterworth filter, and the Shepp and Logan filter, along the short axis, the horizontal long axis and the vertical long axis of the heart. Images were normalized to the maximum count in each image set, and displayed as a color-scale image by a computer system.

Exercise 201Tl SPECT

Each patient performed symptom-limited exercise on a bicycle ergometer in the sitting position. Twelve-lead ECG and blood pressure measurements were obtained at baseline and at every minute of exercise. Endpoints of exercise included excessive fatigue, dyspnea, moderate to severe angina, hypotension, diagnostic ST depression (>1.0 mm horizontal or downsloping, or >2.0 mm upsloping), or significant arrhythmia. At peak exercise, a dose of 111 MBq 201Tl was injected intravenously and the patient was encouraged to exercise for an additional minute. Initial images were obtained immedi-
ately after the termination of exercise and $^{201}$Tl was reinjected and delayed images were obtained 4 h later when $^{201}$Tl was reinjected (Fig 1).

**PET Imaging**

For PET imaging, a Shimadzu-SET 1400 W-10 PET scanner (HEADTOME IV, Shimadzu Corp, Kyoto, Japan) was used to provide 7 slices simultaneously with a 13-mm interval, slice thickness of 11-mm full-width half-maximum (FWHM), and spatial resolution of 4.5-mm FWHM. Axial, 6.5-mm-interval Z-motion of the scanner every minute provided a total of 14 contiguous transverse slices of the myocardium. A 10-min transmission scan was obtained using a rotating germanium-68 rod source. The acquired data were used to correct emission images for body attenuation. We performed $^{18}$F fluorodeoxyglucose positron emission tomography (FDG-PET) by the glucose-loading method. All patients were studied in the fasting state and with 75 g oral glucose loading before imaging. Patients were injected intravenously with 148–407 MBq of FDG. Sixty minutes were allowed for cardiac uptake of FDG and then imaging of glucose utilization was performed for 10 min (Fig 1).

Images were collected in 256×256 matrices and reconstructed by a computer system (Dr. View, Asahi-Kasei Joho System Co Ltd, Tokyo, Japan) using Butterworth and Ramp filters along the short axis, the horizontal axis, and the vertical long axis of the heart. Images were normalized to the maximal count in each image set and were displayed as color-scale images.

**Dobutamine Stress Echocardiography**

All echocardiograms were obtained using a Sonos 2500 (Philips M.S. Co Andover, MA, USA) equipped with a 2.5-MHz transducer. Dobutamine was infused intravenously, starting at a dose of 5 μg/kg body weight per min. The dose was increased to 10 μg/kg per min after 4 min. Echocardiograms were stored on quad-screen before injection and at the end of each stage, as well as being simultaneously recorded on videotape. Twelve-lead ECG and blood pressure were checked every minute. In this study protocol, myocardial viability was assessed at a low dose of dobutamine infusion (10 μg/kg per min).

**Data Analysis**

**Analysis of Dobutamine Stress, Rest and Follow-up Echocardiography** The images were analyzed by 2 independent operators who were unaware of the scintigraphic data. A 13-segment model was used (Fig 2). By visual assessment of endocardial motion and wall thickening, the wall motion abnormality in each segment was classified as...
normal, hypokinetic, akinetic, dyskinetic or hyperkinetic and assigned wall motion scores of 1, 2, 3, 4 and 0, respectively. The left ventricular wall motion index (LVWMI) was calculated before and after revascularization.

For LDDE, we considered an improvement of ≥1 grade in dysynergic segments from rest to low-dose dobutamine infusion as evidence of viability.

Differences in interpretation were resolved by consensus.

Recovery of regional function was defined as an improvement of ≥1 grade between rest and follow-up echocardiograms.

Analysis of SPECT and PET Images

The left ventricle was also divided using the 13-segment model (Fig 2). PET and SPECT images were studied in each segment with echocardiographically dysfunctional areas. FDG and BMIPP uptake was graded using the color map, which color-coded the left ventricular myocardial segments according to their degree of tracer uptake relative to the region with maximal uptake, with semiquantitative division into 10 percentiles. Tracer uptake was graded using a 4-point scale: 1= normal; 2= mildly reduced; 3= moderately reduced; 4= severely reduced or absent. Segments with normal or mildly reduced uptake were considered viable. FDG uptake >50% (grades 1 and 2) was categorized as viable.

Similarly, 201Tl uptake >50% at rest or upon redistribution was categorized as viable.

When the BMIPP score was greater than the 201Tl score by 1, the segment was considered to show mismatched uptake and assumed to be positive for myocardial viability.

The images of SPECT and PET were analyzed by 2 independent operators who were unaware of the clinical and echocardiographic data.

Statistical Analysis

Dichotomous variables were compared by means of χ² statistics or Fisher’s exact test. χ² statistics or Fisher’s test was used to calculate the significance of differences between LDDE and other methods. Differences were considered significant at p<0.05. Statistical analysis was performed with StataView, version 5.0 (SAS Institute, Cary, NC, USA).

Results

Baseline Characteristics

Of the 390 segments analyzed by echocardiography, 110 (28%) had abnormal wall motion, including 68 segments with hypokinesis (62%), 41 segments with akinesis (37%) and 1 segment with dyskinesis (1%).

Several months (5±3 months) after revascularization, 18 of the 41 akinetic and 51 of the 68 hypokinetic segments exhibited improvement.

Assessment of Myocardial Viability and Prediction of Functional Recovery

LDDE

LDDE revealed signs of viable tissue in 73 of the 109 dysynergic segments, and of these 62 revealed wall motion recovery (Table 1). There was improvement in 50 of 51 hypokinetic and 12 of 18 akinetic segments. These findings yielded a sensitivity of 90% and specificity of 80% for predicting functional recovery. The positive predictive value (PPV) and negative predictive value (NPV) for LDDE was 89% and 82%, respectively (Table 2).

FDG-PET

There were 78 of the 109 dysynergic segments that were considered viable by FDG-PET, and 62 of these exhibited improvement (Table 1). The sensitivity and specificity for functional recovery was 90% and 61%, respectively, and the PPV and NPV was 79% and 78%, respectively (Table 2). A total of 20% of grade 3 and 24% of grade 4 segments exhibited functional recovery.

BMIPP

Of the 109 dysynergic segments, 53 were assessed as viable by BMIPP, and 47 of these exhibited improvement (Table 1). The sensitivity and specificity for predicting functional recovery was 67% and 80%, respectively, and the PPV and NPV was 85% and 60%, respectively (Table 2).

RR-Tl SPECT

Of the 109 dysynergic segments, 68 were considered viable by RR-Tl, and 58 of these exhibited improvement (Table 1). The sensitivity and specificity for predicting functional recovery was 84% and 76%, respectively, and the PPV and NPV was 85% and 74%, respectively (Table 2).
RI-Tl SPECT Of the 109 dysynergic segments, 62 were considered viable by RI-Tl, and 51 of these exhibited improvement (Table 1). The sensitivity and specificity for predicting functional recovery was 74% and 73%, respectively, and the PPV and NPV was 82% and 63%, respectively (Table 2).

However, in akinetic segments, there was a significant difference in sensitivity and specificity: LDDE was superior to RR-Tl in sensitivity and to FDG-PET in specificity (Table 1).

Among FDG-PET, RI-Tl, BMIPP and LDDE, there were significant differences in 3 variables (Table 2). In hypokinetic segments, LDDE was superior to RI-Tl and BMIPP in sensitivity and to FDG-PET in specificity.

Representative cases are shown in Figs 4 and 5. A 55-year old man had anterior chest pain and underwent emergency coronary angiography. The LAD was occluded and successful PTCA was performed. According to LDDE, there was no myocardial viability in the antero-septal area, and the lack of myocardial viability in the infarcted area was confirmed by BMIPP, RI-Tl and FDG-PET (Fig 4). In Fig 5, a 71-year old man with anterior chest pain underwent successful emergency PTCA. FDG-PET revealed that there was little myocardial viability in an antero-septal segment, but BMIPP revealed little myocardial viability in either the apical or basal segments of the antero-septal area. On follow-up echocardiography, the basal segments of the antero-septal area showed recovery of wall motion.

Discussion

Differentiation between stunned and necrotic myocardium after AMI is important for predicting functional recovery. Some have compared 201Tl SPECT with LDDE, but there has not been a comparison of FDG-PET, BMIPP, RI-Tl SPECT and RR-Tl SPECT with LDDE in individual patients. In the present study, we compared the ability of each imaging method to detect myocardial viability as a
Detecting Viable Myocardium by DSE, PET and SPECT

Comparison Between SPECT, PET and LDDE

It has been reported that myocardial viability as estimated by regional \(^{18}\)F-fluorodeoxyglucose uptake can accurately differentiate viable myocardial tissue from scarring. A previous study using FDG-PET revealed regional recovery after revascularization and reported a sensitivity of 96% and specificity of 69%.\(^{12}\) We report similar findings of a sensitivity of 90% and specificity of 61% in the present study for predicting improvement of dysynergic segments; however, the specificity of FDG-PET was lower than that of LDDE. The results indicated that FDG-PET detects viability in some infarcted regions that do not have functional improvement after revascularization and this discrepancy can be explained as follows. First, FDG-PET can detect metabolic activity in dysfunctional regions in which only remnants of viable myocardium have survived. These regions may not be able to produce a detectable amount of contraction during LDDE or after revascularization. Second, it may be insufficient to detect functional improvement in successfully revascularized infarct regions. Third, segmental misalignment probably occurs in the comparison.

![Fig 5. Results of LDDE, RI-Tl, RR-Tl, BMIPP and FDG-PET performed in a patient with an antero-septal AMI.](image)
of FDG-PET with LDDE. Fourth, because FDG-PET was used without flow tracer, its specificity is lower.

In some cases, a long time may be required for recovery of myocardial metabolism. In such cases, we were able to detect the contractile reserve of the infarcted region by LDDE despite no detection of viable muscle by FDG-PET. The interval may be insufficient to allow metabolic improvement in successfully revascularized infarct regions. However, we cannot explain why long intervals are needed for recovery of metabolism. It may be necessary to study many cases that have a discrepancy between the LDDE and FDG-PET findings.

BMIPP can predict the reversibility of dysfunctional segments after coronary artery revascularization in patients with a previous MI. Naruse et al have investigated the clinical usefulness of BMIPP imaging in patients with AMI, particularly in the detection of stunned myocardium in those who underwent acute coronary revascularization. In their study, BMIPP showed a higher correlation with wall motion abnormalities by echocardiography in the acute phase than other nuclear imaging tests, whereas delayed \(^{201}\)TI images showed the highest correlation with wall motion abnormalities in the chronic phase. From our data, BMIPP had a higher accuracy in akinetic segments. The incidence of discordant uptake of BMIPP (ie, uptake less than that of \(^{201}\)TI) was significantly higher in myocardial segments than with redistribution \(^{201}\)TI injection SPECT. These same segments showed myocardial viability on LDDE. Dual BMIPP and \(^{201}\)TI myocardial scintigraphy revealed not only myocardial metabolism and perfusion, but also viability.

From our study, dual BMIPP and \(^{201}\)TI myocardial scintigraphy revealed similar diagnostic accuracy. Some studies showed that discordant BMIPP uptake that is less than redistribution \(^{201}\)TI uptake is a potential predictor for functional recovery. The severity score for BMIPP was higher than that for \(^{201}\)TI imaging during the acute stage. This discordant uptake of BMIPP was high in myocardial segments that showed contractile reserve on LDDE.

In the detection of myocardial viability by BMIPP, the hypokinetic segments had less NPV than the akinetic segments. Despite restoration of myocardial perfusion by primary coronary angioplasty, BMIPP uptake is impaired in salvaged myocardium in the acute stage of infarction. Because the metabolism of fatty acid can be influenced by ischemia, the ischemic area with contractile reserve shows a defect on BMIPP. So, BMIPP had low sensitivity and NPV for functional recovery.

Usefulness of LDDE

LBBE has been shown previously to predict improvement of dysfunctional but viable myocardium after revascularization.

With low doses of dobutamine, we can detect contractile reserve in dysfunctional myocardium because dobutamine is a synthetic \(\beta\)-agonist. However, there is a problem that even low doses of dobutamine may induce myocardial ischemia, although Sun et al have recently shown that dobutamine increases coronary blood flow and none of the present patients had restenosis or reocclusion of the culprit vessel at follow-up. Therefore, we consider that low dose dobutamine can detect myocardial viability in dysfunctional areas without ischemia.

Smart et al studied 63 patients at 2 days after MI and in 19 of 22 patients LDDE correctly predicted the improvement in regional function. Other studies have revealed that LDDE is effective for evaluation of myocardial viability and the results of our study also demonstrate that LDDE can predict functional recovery after myocardial infarction. Importantly, LDDE can detect functional recovery of viable myocardium, whereas FDG-PET, BMIPP and \(^{201}\)TI-SPECT could detect myocardial viability by changes in metabolic activity. BMIPP had a low sensitivity for detection of myocardial viability. FDG-PET had similar sensitivity, but lower specificity than LDDE because the amount of viable myocardial tissue that exhibited metabolic activity was not sufficient for detecting contractile reserve.

Between FDG-PET, RI-TI, BMIPP and LDDE, there were significant differences in 3 variables (Table 2). In akinetic segments, LDDE is superior to RR-TI in sensitivity (Table 1).

In fact, positron emission tomographic facilities are not widely available because of their high operating costs, whereas LDDE is relatively low cost.

Study Limitations

Our study is limited by the small number of patients. In LDDE, visual assessment is used for the wall motion analysis, so when there is a minor change in wall motion during dobutamine infusion, this method of detection may be relatively insensitive. When the echocardiographic images are unclear, we can not evaluate myocardial viability. Another problem is the segmental difference of alignment between LDDE and the other methods. Misalignment between the different techniques is a problem in a comparison of several techniques.

Conclusion

LDDE could detect functional recovery of viable myocardium at a relative early period of AMI as well as FDG-PET, \(^{201}\)TI-SPECT and BMIPP. However, LDDE is more effective for evaluation of myocardial viability, because it has higher sensitivity and specificity than the other methods.

References

Detecting Viable Myocardium by DSE, PET and SPECT


