Contractile Reserve, Thallium-201 Reverse Redistribution and Mismatch Between Perfusion and Metabolism in Reperfused Infarct-related Myocardium With Delayed and Incomplete Functional Recovery

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SUMMARY

We investigated simultaneously the correlations between dobutamine-induced contractile reserve (CC), thallium-201 reverse redistribution (RR) and a mismatch between perfusion and metabolism (MM) to the magnitude of functional recovery.

In 32 patients with coronary angioplasty early after infarction, echocardiography was performed at low-dose dobutamine stress within 1 week and at resting state at 1 month. Thallium-201/iodine-123 β-methyl-iodophenyl pentadecanoic acid (BMIPP) dual-isotope single photon emission tomography was performed at 1 month. Wall motion and the uptake of each tracer were scored as 0 to 2 in the infarct-related segments, and CC, RR, and MM were evaluated in the infarct-related segments.

In 71 akinetic or dyskinetic segments before reperfusion, the initial thallium-201 uptake and initial BMIPP uptake scores and the 4 hour redistribution thallium-201 uptake scores were less severe in the group with complete functional recovery (group A), followed by the group with incomplete recovery (group B) and then the group with no recovery (group C) (each P < 0.0001). CC was the greatest in group A, followed by group B, and then group C (76.2% in 16/21, 60% in 15/25, 36% in 9/25, P = 0.0212). RR and MM were greater in group B (52% in 13 and 64% in 16) than in groups A and C (19% in 4 and 8% in 2, 33.3% in 7 and 24% in 6, P = 0.0013 and P = 0.0113).

The intensity of functional damage reflects perfusion and metabolism, but the delayed and incomplete functional recovery after reperfusion may be closely related to RR, MM, and CC. (Jpn Heart J 2004; 45: 739-748)

Key words: SPECT, Reverse redistribution, Mismatch of perfusion and metabolism, Contractile reserve, PTCA
The aim of reperfusion therapy of an infarct-related coronary artery after acute myocardial infarction is to preserve left ventricular function by achieving myocardial salvage. Early reperfusion of the occluded coronary results in the complete functional recovery immediately, but Braunwald and Kloner described reversibly-injured stunned myocardium which returns completely to normal function after some days or a week. Boden, et al reported intensely injured infarct-related segments, which represent “maimed stunning myocardium”, display the incomplete functional recovery finally, but the effectiveness of reperfusion may be established after some weeks or a month. However, the optimal approaches for identifying maimed myocardium have not been clarified in the clinical setting.

Although contractile reserve with dobutamine, reverse redistribution with thallium-201 single photon emission computed tomography (SPECT) imaging at rest or under stress protocols, and a mismatch of metabolism based on iodine-123 \( \beta \)-methyl-iodophenyl pentadecanoic acid (BMIPP) SPECT imaging, as myocardial free fatty acid metabolism to perfusion tracer all indicate the presence of viable myocardium, these 3 parameters have not been evaluated simultaneously in maimed myocardium with incomplete functional recovery. The aim of this study was to clarify whether the infarct-related maimed myocardium with delayed and incomplete functional recovery could be identified using dobutamine-induced contractile reserve, thallium-201 reverse redistribution, and a mismatch between perfusion and metabolism.

**Methods**

**Study patients:** Thirty-two patients (60.3 ± 10.4 years) with a first acute myocardial infarction were selected for primary percutaneous transluminal coronary angioplasty (PTCA) without thrombolytic therapy. Acute myocardial infarction was diagnosed by persistent symptoms of chest pain lasting more than 30 minutes, ST segment elevations of more than 1 mm in at least 2 contiguous leads on an ECG, and elevated creatine kinase (4018 ± 3049, range, 427 to 14,340). These patients met the following conditions: an onset-to-admission interval of ≤ 6 hours, persistent ischemic chest pain or hemodynamic compromise at an interval of > 6 hours, and significant stenosis of an infarct-related vessel. The patients underwent successful PTCA (without stenting) with Thrombolysis In Myocardial Infarction (TIMI) trial grade III flow, and the infarct-related coronary artery had a residual diameter stenosis of less than 50% after PTCA. Written informed consent was obtained from all patients.

**Cardiac catheterization:** The patients underwent cardiac catheterization immediately before PTCA and more than 3 months after PTCA, which included coronary
angiography and left ventriculography to assess left ventricular function. All patients had no restenosis of the infarct-related coronary artery as determined by a follow-up coronary angiography after PTCA. The diameters of the stenotic areas of the involved coronary artery segments were classified visually according to the American Heart Association guidelines.

**Dobutamine echocardiography:** Two-dimensional echocardiography was performed with a commercially available system (HDI 5000, ATL Co., Washington, USA) during dobutamine loading after overnight fasting within 1 week after PTCA (4.9 ± 1.5 days). Patients were positioned in the left oblique lateral decubitus position, and the four standard views (left parasternal long- and short-axis and apical four- and two-chamber views) were obtained continuously at baseline and during intravenous infusion of dobutamine in two 5-minute periods of 5 and 10 µg/kg/minute (total of 10 minutes). A 12-lead ECG was in place during stress and for 10 minutes of recovery, and heart rate and blood pressure were monitored every minute. Echocardiographic regional wall motion abnormalities were evaluated using a model in which the left ventricle was divided into 9 segments (short axis images) to correspond with the SPECT images. Regional wall motion, including systolic thickening, was visually scored as follows: 0 = normal, 1 = hypokinesis, and 2 = akinesis or dyskinesis. A decrease of one grade or more of the reduced wall motion score on an echocardiographic image during dobutamine with a baseline image was considered evidence of contractile reserve. Echocardiograms were repeated at rest without pharmacological infusion at 1 month after PTCA. Echocardiograms were interpreted by two investigators without knowledge of the clinical or scintigraphic data. Agreement between the observers was 95%, and discrepancies were resolved by consensus.

**Thallium-201 / I-123 BMIPP dual-isotope SPECT:** Dual-isotope SPECT was performed at rest at 1 month after PTCA (25.8 ± 5.4 days). After 3 mCi (111 MBq) of iodine-123 BMIPP and 3 mCi (111 MBq) of thallium-201 were injected intravenously in order and flushed with normal saline solution, SPECT images were obtained at 20 minutes (initial images with thallium-201 and I-123 BMIPP) and 4 hours (resting redistribution images with thallium-201) after injection. Cardiac SPECT images were acquired on a dual-detector, rotating, dedicated cardiac camera (Prizm 2000XP, Picker Co., Philadelphia, USA) equipped with a low-energy, high-resolution collimator and interfaced with an Odyssey computer (Picker Co.). Two energy windows were selected for dual-isotope SPECT imaging using the two tracers: the 159-keV photopeak of I-123 with a 20% window and the 75-keV photopeak of thallium-201 with a 20% window. No downscatter correction was performed. The reconstructed transaxial slices were then reoriented into the vertical long, horizontal long, and short axes. Short-axis SPECT images were divided into an apex, a middle, and a basal level, with the
last 2 levels further divided into 4 additional areas, thereby yielding a total of 9 regions. An abnormality was considered to be present if the % uptake of the radioactive count in the regional areas was 2.5 standard deviations below the mean normal limit in each myocardial area of the left ventricle, as shown in a previous study.9) Furthermore, the abnormal infarct-related segments were quantitatively scored to 3 grades8) as follows; 1 for a ≤ 10% decrease or 2 for a > 10% decrease of tracer uptake in the myocardium. Segments with no abnormality of tracer uptake were scored as 0 (normal).

An increase of one grade or more of the uptake score on the initial thallium-201 image compared to the 4 hour resting redistribution image was considered to be evidence of redistribution, and a decrease of one grade or more of the uptake score on the initial thallium-201 image was considered to be evidence of reverse redistribution. A decrease of one grade or more of the uptake score on the thallium-201 image compared to the I-123 BMIPP image was considered as evidence of a mismatch of perfusion and metabolism (Figure 1).

Figure 1. Polar map images; A: resting initial thallium-201 image, B: resting initial I-123 β-methyl-iodophenyl-pentadecanoic acid image, C: 4 hour redistribution thallium-201 image. Low dose dobutamine induced contractile reserve in a patient (60 year-old female) who underwent percutaneous transluminal coronary intervention (PTCA) early after acute myocardial infarction. Both thallium-201 and BMIPP images showed resting reverse redistribution with thallium-201 and a mismatch of defect size between initial thallium-201 and I-123 BMIPP images. At 1 month after PTCA, the wall motion recovered incompletely from the akinesis to hypokinesis in the infarct-related myocardium.
Statistical analysis: Comparisons between groups were performed using a one-way analysis of variance (ANOVA) for continuous variables and the chi-square test for categorical variables (χ² test). A P value of less than 0.05 was considered to be statistically significant. All data are presented as the mean ± 1 standard deviation.

RESULTS

Cardiac catheterization: Of 32 patients, the involved infarct-related coronary artery was the left anterior descending artery in 21 patients, the right coronary artery in 9, and the left circumflex artery in 2. Twenty-two patients had single vessel disease and 10 patients had multivessel disease. Left ventricular ejection fraction was 46.9 ± 13.2% before PTCA and was improved to 53.5 ± 12.6% at 3 months after PTCA (P = 0.0019).

Low dose dobutamine stress testing: In the acute phase, during low-dose dobutamine stress, heart rate, systolic blood pressure, and the rate pressure product increased by a mean of 22.7%, 4.5%, and 28.3%, respectively, at the maximum dose of dobutamine (rest: heart rate; 74 ± 15, blood pressure; 117 ± 17/71 ± 10, stress: heart rate; 91 ± 18, P < 0.0001, blood pressure; 122 ± 24/65 ± 15, P = NS).

Magnitude of functional recovery: As shown in Figure 2, 71 infarct-related segments with akinesis or dyskinesis of wall motion before PTCA were classified on the basis of the magnitude of wall motion at 1 month after PTCA: the 21 segments with normal wall motion (complete functional recovery), 25 segments with hypokinetic wall motion (incomplete functional recovery), and 25 segments with akinetic or dyskinetic wall motion (no functional recovery).

Figure 2. The infarct-related segments with akinetic or dyskinetic wall motion before PTCA were divided into 3 groups on the basis of the magnitude of regional wall motion at 1 month after PTCA as follows: the group with complete functional recovery, the group with incomplete recovery, and the group with no functional recovery.
At 1 month after PTCA, the initial thallium-201 uptake and initial I-123 BMIPP uptake scores, and 4 hour redistribution thallium-201 uptake scores were less severe in the group with complete functional recovery, followed by the group with incomplete recovery and the group with no recovery (initial thallium-201; 0.2 ± 0.6 scores, 0.5 ± 0.7, 1.7 ± 0.6, $P < 0.0001$, initial BMIPP; 0.7 ± 0.9, 1.4 ± 0.9, 1.9 ± 0.3, $P < 0.0001$, 4 hour redistribution thallium-201; 0.4 ± 0.6, 1 ± 0.9, 1.7 ± 0.5, $P < 0.0001$, respectively) (Figure 3).

**Contractile reserve, reverse redistribution, and perfusion-metabolism mismatch:** As shown in Figure 4, the presence of contractile reserve with dobutamine stress was the greatest in the group with complete functional recovery, followed by the group with incomplete recovery as compared to the group with no recovery (76.2% (16 of 21 segments) in the group with complete functional recovery, 60% (15 of 25) in the group with incomplete functional recovery, and 36% (6 of 25), in the group with no functional recovery, respectively, $P = 0.0212$). The presence of reverse redistribution and the presence of a perfusion-metabolism mismatch were greater in the group with incomplete functional recovery than in the group with complete recovery and the group with no recovery (19% (4 of 21 segments) with complete recovery, 52% (13 of 25 segments) with incomplete recovery, 8%
We identified the infarct-related maimed myocardium with delayed and incomplete functional recovery after reperfusion using contractile reserve under dobutamine infusion, the reverse redistribution of thallium-201 uptake, and the mismatch of myocardial perfusion and free fatty acid metabolism. The reverse redistribution and perfusion-metabolism mismatch were remarkable, despite the preserved contractile reserve in the maimed myocardium.

Although previous studies have demonstrated that the incomplete functional recovery after reperfusion following acute coronary syndrome often occurs with a time course to reperfusion later than the time limit for the recovery to normal wall motion, recent studies have reported that adequate myocardial tissue perfusion after successful reperfusion may be more essential for functional recovery.
than is the patency or the time to reperfusion of the infarct-related coronary artery, and that the maimed myocardium with delayed and incomplete functional recovery occurs concomitantly in myocardial regions different from the infarct-related myocardium with complete recovery or the necrotic myocardium with no functional recovery in a patient with an acute coronary syndrome after early reperfusion of an infarct-related coronary artery.

Hashimoto, et al speculated that the time course and magnitude of postischemic functional recovery depend on the severity of ischemia-reperfusion-induced myocardial injury, and that both necrotic myocardium and salvaged but stunned myocardium could interact with each other and contribute to prolonged postischemic contractile failure. Our results indicate that the myocardial damage persisted in the infarct-related myocardium with incomplete functional recovery despite early reperfusion of the infarct-related coronary artery compared to the myocardium with complete functional recovery.

Reverse redistribution with thallium-201 may evaluate myocardial viability based on microvascular integrity, particularly in the resolution of coronary artery stenosis after myocardial infarction. Resting reverse redistribution with thallium-201 uptake is caused by the increased washout of thallium-201 uptake in reperfused myocardium, such as stunned myocardium. In these myocardial segments, interstitial edema after injury also is responsible for increased thallium-201 influx and early washout, resulting in reverse redistribution. Faraggi, et al demonstrated that in patients with acute myocardial infarction in whom early and complete recanalization of infarct-related vessels was shown by TIMI grade 3 flow, there was a close relation among the thallium-201 reverse redistribution, recovery of microvascular perfusion, and functional recovery. Recent studies have reported that reverse redistribution depends on the preserved regional flow by either through patent coronary arteries or collaterals in patients following thrombolytic therapy. One of the mechanisms of reverse redistribution is a faster washout of thallium-201 in this area than the normal remote areas, which may result from the higher blood flow supplied by the patent coronary artery in the reperfused areas than the normal blood flow. On the other hand, impaired free fatty acid metabolism is correlated with ischemia-induced cardiac dysfunction. The mismatched appearance of thallium imaging and fatty acid imaging in the salvaged myocardium was closely related to perfusion contraction mismatch, and predicted the postischemic function recovery. A mismatch of perfusion and metabolism underlying postischemic dysfunction is caused by impairment of energy production and utilization.

The infarct-related maimed myocardium with incomplete functional recovery which preserved the contractile reserve indicates the persistent damage of energy production and utilization caused by the injured cell membrane integrity.
at the mitochondrial level after recovery of the microvascular system at the capillary level following the early reperfusion.

The clinical significance of stunned myocardium is beginning to be appreciated by clinicians. Furthermore, the magnitude of prospective functional recovery in the viable myocardium predicts the prognosis. The viable but infarct-related maimed myocardium with incomplete functional recovery may cause hemodynamic instability requiring intensive monitoring and pharmacological or mechanical support. Furthermore, the development of pharmacological agents may hasten the recovery from the maimed myocardium. We propose that the recognition and diagnosis of maimed myocardium with delayed and incomplete functional recovery are important from a practical standpoint and may impact patient management.

Study limitation: Differences in tissue attenuation between I-123 and thallium-201 uptakes were potential limitations of this study, and methods for downscatter correlation have not been established. However, recent studies have demonstrated that simultaneous dual-isotope imagings of these tracers without downscatter compensation are feasible with acceptable accuracy in clinical studies.

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REFERENCES


