Myocardial Perfusion and Fatty Acid Metabolism in Patients With Tako-Tsubo-Like Left Ventricular Dysfunction

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OBJECTIVES
We sought to assess myocardial perfusion and metabolism in patients with peculiar transient asynergy, which consisted of basal normokinesia and apical akinesia of the left ventricle (LV) at the same time.

BACKGROUND
This asynergy has been widely called “tako-tsubo-like LV dysfunction” in Japan, but little is known about its pathophysiology.

METHODS
We performed rest tllium-201 (201Tl) and iodine-123-beta-methyl-p-iodophenyl pentadecanoic acid (123I-BMIPP) dual-isotope myocardial single-photon emission computed tomography (SPECT) in 14 patients with tako-tsubo-like LV dysfunction. The LV was divided into 17 segments, and each segment was graded with scores between normal uptake (0) and defect (4). We also measured the Thrombolysis in Myocardial Infarction trial (TIMI) frame count in 28 patients and 20 control subjects.

RESULTS
Early SPECT (5±3 days) revealed that the total defect score value with BMIPP was significantly higher than reduced uptake with 201Tl (p<0.01). Reduced uptake of BMIPP was observed in parallel with an apical akinetic region and usually involved uptake of 201Tl. This discrepancy improved gradually during the follow-up period (29±6 days) (p=0.36). Compared with control subjects, patients had a TIMI frame count that was significantly higher in all coronary arteries immediately after onset. This higher TIMI frame count decreased but was sustained even after resolution of tako-tsubo-like LV dysfunction.

CONCLUSIONS
Our data suggest that myocardial fatty acid metabolism is more severely impaired than myocardial perfusion, in parallel with an apical akinetic region during the early phase, and that impaired multivessel coronary microcirculation is involved, at least in part, in tako-tsubo-like LV dysfunction. (J Am Coll Cardiol 2003;41:743–8) © 2003 by the American College of Cardiology Foundation

We have recently reported a novel cardiac syndrome exhibiting transient left ventricular (LV) dysfunction with chest symptoms, electrocardiographic changes, and minimal myocardial enzymatic release mimicking acute myocardial infarction (MI), but without significant coronary artery disease (CAD) (1–4). Because early left ventriculography revealed basal normokinesia and apical akinesia at the same time, and the end-systolic ventriculogram looked like a “tako-tsubo” used for trapping octopuses in Japan, we originally proposed the term “tako-tsubo-like LV dysfunction” in 1990 (2). This syndrome has been widely recognized in Japan, and several case reports (5–11) and a multicenter study (12) have recently shown some of the clinical features, including a predominance of elderly women, as well as a favorable prognosis. The angiographic main findings were: 1) LV asynergy extended over more than one coronary artery region and was quite different from that in acute MI; 2) this asynergy was localized to the apical region; and 3) this asynergy was dramatically resolved in a short time. However, little is known about its pathophysiology, partly because the condition was rare.

In the current study, first we assessed the time course of myocardial perfusion and fatty acid metabolism in patients with tako-tsubo-like LV dysfunction by using serial rest tllium-201 (201Tl) and iodine-123-beta-methyl-p-iodophenyl pentadecanoic acid (123I-BMIPP) dual-isotope myocardial single-photon emission computed tomography (SPECT). Second, to determine whether coronary blood flow was impaired in all coronary arteries, in agreement with LV asynergy, we measured the Thrombolysis In Myocardial Infarction trial (TIMI) frame count, an index of coronary blood flow, representing the number of frames required for contrast material to reach standardized distal landmarks (13,14).

METHODS
Study protocol 1: 201Tl and 123I-BMIPP myocardial SPECT in tako-tsubo-like LV dysfunction. SUBJECTS. We studied 14 Japanese patients with tako-tsubo-like LV dysfunction who underwent emergency angiography within 24 h after onset. Tako-tsubo-like LV dysfunction was defined as basal normokinesia and apical akinesia on the early left ventriculogram, without significant CAD, which extended over more than one coronary artery region (1). Patients with idiopathic cardiomyopathy, a previous MI, a
cerebrovascular accident, or pheochromocytoma were excluded from this study. The study protocol was approved by our hospital's Committee on Ethics.

Contrast left ventriculography and coronary angiography were performed by the femoral or brachial approach after intravenous infusion of 3,000 U heparin. Left ventriculography was performed in the 30° right anterior oblique projection. The LV ejection fraction, end-diastolic volume, and end-systolic volume were calculated by means of the area-length method. Coronary artery disease was defined as >50% reduction in the lumen diameter of the major epicardial coronary artery.

Blood samples were obtained every 3 h during the first 24 h and once daily from the second day to determine the peak creatine kinase level.

₂⁰¹Tl AND ¹²³I-BMIPP MYOCARDIAL SPECT. Rest ₂⁰¹Tl and ¹²³I-BMIPP dual-isotope myocardial SPECT was performed about five days after onset. In some of the patients, it was repeated about two and four weeks later. After overnight fasting, an intravenous bolus injection of ₂⁰¹Tl (111 MBq) and ¹²³I-BMIPP (111 MBq) was performed at rest, and data acquisition was started 20 min after radiotracer injection using a three-headed SPECT system with low-energy, all-purpose, parallel-hole collimators. A total of 60 projection images was obtained in a 128 × 128 matrix over 360°, with 30 s per view. After reduction of the matrix size of the projection data to 64 × 64, tomographic images along the vertical long and horizontal long and short axes were created with a Shepp and Logan filter. The SPECT image of the LV was divided into 17 segments for quantitative analysis. Short-axis slices were separated into eight segments at the basal and midventricular levels. The apical portion of one segment was evaluated on vertical long-axis slices. Neither crosstalk correction between ₂⁰¹Tl and ¹²³I-BMIPP nor downscatter correction was performed. Each segment was graded visually with scores between 0 and 4 (0 = normal uptake; 1 = mildly reduced; 2 = moderately reduced; 3 = severely reduced; 4 = defective) in a blinded manner by the three experienced cardiologists (S.K., Y.S., and K.N.). The sum of each score was defined as the total defect score (TDS), reflecting the severity of impaired myocardial perfusion or impaired fatty acid metabolism.

Study protocol 2: TIMI frame count in tako-tsubo-like LV dysfunction. SUBJECTS. We studied 28 Japanese patients with tako-tsubo-like LV dysfunction and 20 control subjects with atypical chest pain and a normal coronary angiogram. Inclusion and exclusion criteria of tako-tsubo-like LV dysfunction were the same as stated in protocol 1. All patients in protocol 1 were included in protocol 2.

TIMI frame count. Coronary angiograms were recorded at 25 frames/s on a 35-mm cine frame for subsequent off-line analysis. Briefly, the TIMI frame count method, an index of coronary blood flow, estimates the number of frames required by contrast material to opacify standard predetermined distal coronary landmarks (13,14), and its value has been recently validated (15–17). The TIMI frame count on each angiogram was calculated as the mean value obtained by the two experienced cardiologists (S.K. and K.N.).

Statistical analysis. Data are expressed as the mean value ± SD. The paired Student t test was used to compare the two sequential values during follow-up. The unpaired Student t test was used to compare TIMI frame counts between patients with tako-tsubo-like LV dysfunction and control subjects. The chi-square test and Fisher exact test were used to compare categorical data. Differences were considered significant at p < 0.05.

RESULTS

Study protocol 1: patient characteristics. The clinical and angiographic characteristics in the 14 patients with tako-tsubo-like LV dysfunction are summarized in Table 1. All patients were female, ranging in age from 55 to 84 years (mean 72 ± 9). None of the patients had diabetes, but five patients had systemic hypertension and five had previous angina. Five patients had emotional stress and two had physical stress as the trigger event. Early left ventriculography was performed in all patients within 24 h, and follow-up left ventriculography was performed in 10 patients at 12 ± 5 days after onset. Early left ventriculography revealed tako-tsubo-like LV dysfunction, and this asynergy was dramatically resolved on the follow-up left ventriculo-

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<thead>
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<th>Table 1. Protocol 1: Patient Characteristics (n = 14)</th>
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<td>Female gender</td>
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<td>Age (yrs)</td>
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<td>Prior angina</td>
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<td>Peak CK (IU/l)</td>
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<td>LVEF (%)</td>
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<td>LVEDV (ml)</td>
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<td>LVESV (ml)</td>
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Data are presented as the mean value ± SD or number (%) of patients.

CK = creatine kinase; LVEF = left ventricular ejection fraction; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume.
gram or echocardiogram in all patients. The LV ejection fraction improved significantly from \(53 \pm 10\%\) to \(67 \pm 12\%\) (\(p < 0.01\)).

**SPECT studies (Figs. 1 and 2).** An early SPECT image was obtained in all patients at \(5 \pm 3\) days after onset. The TDS value with \(^{123}\)I-BMIPP was significantly higher than reduced uptake with \(^{201}\)Tl (5.4 \pm 5.9 vs. 18.7 \pm 8.6, \(p < 0.01\)). Reduced uptake of \(^{201}\)Tl was observed within the apical region. Reduced uptake of \(^{123}\)I-BMIPP was observed in parallel with an apical akinetic region and usually involved uptake of \(^{201}\)Tl.

A subsequent SPECT image was obtained in eight patients 8 days after admission. Although reduced uptake of \(^{201}\)Tl improved at 15 days, reduced uptake of \(^{123}\)I-BMIPP was sustained even after resolution of tako-tsubo-like LV dysfunction.

**Figure 1.** Time course of myocardial perfusion and fatty acid metabolism assessed by serial rest \(^{201}\)Tl and \(^{123}\)I-BMIPP dual-isotope myocardial single-photon emission computed tomography performed at \(5 \pm 3\) days (acute phase), \(15 \pm 3\) days (subacute phase), and \(29 \pm 6\) days (follow-up) after onset. Myocardial fatty acid metabolism was more severely impaired than myocardial perfusion during the early phase and improved gradually during follow-up.

**Figure 2.** Time course of left ventriculograms (top panel) and single-photon emission computed tomography (SPECT) images (bottom panel) in a patient with tako-tsubo-like left ventricular (LV) dysfunction. Tako-tsubo-like LV dysfunction complicated by a pressure gradient of 70 mm Hg through the LV outflow tract and moderate mitral regurgitation was dramatically resolved after 14 days. In this case, early SPECT revealed similarly reduced uptake between \(^{201}\)Tl and \(^{123}\)I-BMIPP at eight days. Although reduced uptake of \(^{201}\)Tl improved at 15 days, reduced uptake of \(^{123}\)I-BMIPP was sustained even after resolution of tako-tsubo-like LV dysfunction. ED = end-diastole; ES = end-systole; LCA = left coronary artery.
patients at 15 ± 3 days when tako-tsubo-like LV dysfunction was already resolved on the follow-up left ventriculogram or echocardiogram. The TDS value with $^{123}$I-BMIPP tended to be higher than that with $^{201}$TI (3.2 ± 3.3 vs. 9.8 ± 7.6, p = 0.11).

Follow-up SPECT was obtained in three patients at 29 ± 6 days, and there was no significant difference in the TDS value between $^{201}$TI and $^{123}$I-BMIPP (2.7 ± 2.3 vs. 5.7 ± 4.5, p = 0.36).

**Study protocol 2: patient characteristics.** The clinical and angiographic characteristics in the 28 patients with tako-tsubo-like LV dysfunction and in the 20 control subjects with atypical chest pain and a normal coronary angiogram (control group) are summarized in Table 2. All patients were female, ranging in age from 55 to 84 years (mean 70 ± 8). Two patients had diabetes; 11 patients had systemic hypertension; and 13 patients had previous angina. Seven patients had emotional stress, and three had physical stress as the trigger event. Early left ventriculography was performed in all patients within 24 h, and follow-up left ventriculography was performed in 22 patients at 11 ± 4 days. Early left ventriculography revealed tako-tsubo-like LV dysfunction, and this asynergy was dramatically resolved on the follow-up left ventriculogram or echocardiogram in all patients. The LV ejection fraction improved significantly from 49 ± 12% to 69 ± 12% (p < 0.01).

**TIMI frame count (Fig. 3).** Early coronary angiography was performed in all patients. The TIMI frame count was 63 ± 24 in the left anterior descending coronary artery (LAD), 42 ± 15 in the left circumflex artery (LCx), and 48 ± 16 in the right coronary artery (RCA). Follow-up angiography was performed in 20 patients at 11 ± 4 days when tako-tsubo-like LV dysfunction was almost resolved. The TIMI frame count decreased significantly to 47 ± 13 in the LAD (p < 0.01), to 36 ± 10 in the LCx (p < 0.05), and to 37 ± 8 in the RCA (p < 0.01). However, compared with control subjects, the TIMI frame count was significantly higher in all coronary arteries, even after resolution of tako-tsubo-like LV dysfunction.

### Table 2. Protocol 2: Patient Characteristics

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<tr>
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<th>Tako-Tsubo Group (n = 28)</th>
<th>Control Group (n = 20)</th>
<th>p Value</th>
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<tr>
<td>Female gender</td>
<td>28 (100%)</td>
<td>20 (100%)</td>
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</tr>
<tr>
<td>Age (yrs)</td>
<td>70 ± 8</td>
<td>69 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2 (7%)</td>
<td>2 (10%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11 (39%)</td>
<td>9 (45%)</td>
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<td>Prior angina</td>
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<td>Peak CK (IU/l)</td>
<td>567 ± 645</td>
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<td></td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>49 ± 12</td>
<td>63 ± 6</td>
<td>&lt;0.01</td>
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<tr>
<td>LVEDV (ml)</td>
<td>109 ± 24</td>
<td>111 ± 25</td>
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<td>LVESV (ml)</td>
<td>53 ± 20</td>
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<td>&lt;0.01</td>
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Data are presented as the mean value ± SD or number (%). Other abbreviations as in Table 1.

**DISCUSSION**

**Present findings.** By using rest $^{201}$TI and $^{123}$I-BMIPP dual-isotope myocardial SPECT, we demonstrated the following: 1) myocardial fatty acid metabolism was more severely impaired than myocardial perfusion during the early phase; 2) this discrepancy between myocardial perfusion and fatty acid metabolism improved gradually during follow-up; and 3) impaired myocardial fatty acid metabolism was usually sustained, even after resolution of tako-tsubo-like LV dysfunction. In addition, by using the TIMI frame count method, we demonstrated that coronary blood flow was severely impaired in all coronary arteries, in agreement with LV asynergy immediately after onset, and that coronary blood flow improved but the impairment was sustained even after resolution of tako-tsubo-like LV dysfunction.

**Previous findings of tako-tsubo-like LV dysfunction.** Even in Japan, there have been few reports assessing myocardial perfusion or metabolism in patients with tako-tsubo-like LV dysfunction by using myocardial SPECT. In
addition, almost all reports have presented only a small number of patients, because the condition was rare (9–11). Ito et al. (10) examined seven patients with tako-tsubo-like LV dysfunction without significant CAD by using serial technetium-99m-tetrofosmin myocardial SPECT. They demonstrated that intracoronary nicorandil reduced ST-segment elevation during the early phase and that myocardial perfusion was impaired immediately after hospital admission but almost improved after three to five days. From these results, they speculated that an impaired coronary microcirculation might be one causative mechanism of tako-tsubo-like LV dysfunction. In 1996, Gibson et al. (13) introduced the TIMI frame count method for measuring coronary flow velocity from coronary angiograms. This measurement has been significantly correlated with flow velocity measured with the Flowire (Cardiometrics Inc., Mountain View, California) by several investigators (15). We applied this technique to measure coronary flow velocity in patients with tako-tsubo-like LV dysfunction, and first we demonstrated that coronary blood flow was severely impaired in all coronary arteries immediately after onset. This finding was consistent with peculiar asynergy, which seemed to extend over more than one coronary artery region. It remained unclear whether impaired multivessel coronary blood flow was a cause or effect of tako-tsubo-like LV dysfunction. However, in the current study, we also demonstrated that coronary blood flow improved, but the impairment was sustained even after resolution of tako-tsubo-like LV dysfunction. This finding suggests that impaired multivessel coronary blood flow was, at least in part, a cause of tako-tsubo-like LV dysfunction.

Discrepancy between myocardial perfusion and fatty acid metabolism. In the normal myocardium under aerobic conditions, 70% to 80% of the energy source of myocardial utilization is dependent on beta-oxidization of fatty acids. In ischemic conditions, beta-oxidization in the mitochondria is immediately reduced, and alternations of fatty acid utilization persist in the postischemic myocardium as ischemic memory (18). Iodine-123-BMIPP is one of the most commonly used clinical tracers in Japan and some European countries because of its high extraction and retention in the myocardium (19–21). In the current study, by using rest $^{201}$TI and $^{123}$I-BMIPP dual-isotope myocardial SPECT, we demonstrated that a discrepancy between myocardial perfusion and fatty acid metabolism was often observed during the early phase of tako-tsubo-like LV dysfunction. In fact, in the setting of acute MI, Tamaki et al. (19) previously reported that uptake of $^{123}$I-BMIPP was occasionally more reduced than that of $^{201}$TI, particularly after successful reperfusion therapy, and that this discrepancy was often observed in more salvaged myocardium after severe ischemia—in other words, more stunned myocardium (22). Thus, our results, combined with the results of certain published clinical reports, suggest that tako-tsubo-like LV dysfunction may essentially be stunned myocardium.

Mechanism of impaired coronary blood flow. Factors that govern coronary blood flow are complex and include epicardial coronary artery lumen diameter, vasospasm, anterograde perfusion pressure, and microvascular circulation. However, in the current study, no patients had flow-limiting stenosis, vasospasm, or systemic hypotension during angiography to measure the TIMI frame count. Reduced coronary blood flow is sometimes observed after emergency or elective angioplasty and is called the no-reflow phenomenon (23–25). The mechanism of the no-reflow phenomenon is not clear. Several mechanisms have been advocated for the no-reflow phenomenon in animal models, including direct ischemic microvascular injury with endothelial cell swelling, microvascular obstruction by leukocyte plugging or thrombi, and increased vasomotor tone. We could not determine the precise cause of tako-tsubo-like LV dysfunction in the current study. However, from our results, we believe that impaired multivessel coronary microcirculation is one causative mechanism of tako-tsubo-like LV dysfunction.

Study limitations. This is a retrospective study, and there are several limitations of this study. First, we did not systematically perform serial myocardial SPECT studies in all of our patients, partly because some patients were discharged within 10 days after onset and follow-up was incomplete. Second, the number of patients was low, especially at follow-up, but the condition of tako-tsubo-like LV dysfunction was rare. Third, the difference in tissue attenuation between $^{201}$TI and $^{123}$I-BMIPP was a potential limitation of this study, and methods for downsccatter correction have not been established. Because quantitative analyses often reveal more reduced uptake of $^{201}$TI than that of $^{123}$I-BMIPP in the septal and inferior regions as a result of the difference in photon attenuation between these two tracers, we used a visual semiquantitative scoring system. Finally, we did not routinely measure the TIMI frame count after administration of intracoronary verapamil, papaverine, or nicorandil, which had a dilating effect on coronary microvessels.

Several questions also remain. Why is LV asynergy localized to the apical region? Why does tako-tsubo-like LV dysfunction develop predominantly in elderly females? Further studies are necessary to clarify these questions about tako-tsubo-like LV dysfunction.

Conclusions. Myocardial fatty acid metabolism was more severely impaired than myocardial perfusion, in parallel with an apical akinetic region during the early phase, and this discrepancy between myocardial perfusion and fatty acid metabolism improved gradually during follow-up in patients with tako-tsubo-like LV dysfunction. Impaired myocardial fatty acid metabolism was usually sustained, even after resolution of an apical wall motion abnormality. In addition, our results, combined with the results of certain published clinical reports, suggest that tako-tsubo-like LV dysfunction may essentially be stunned myocardium due to impaired multivessel coronary microcirculation.
REFERENCES


