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Assessment of Takotsubo cardiomyopathy (transient left ventricular apical ballooning) using ^{99m}Tc-tetrofosmin, ^{123}I-BMIPP, ^{123}I-MIBG and ^{99m}Tc-PYP myocardial SPECT

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We compared Takotsubo cardiomyopathy (transient left ventricular apical ballooning) with acute myocardial infarction (AMI) using two-dimensional echocardiography, ^{99m}Tc-tetrofosmin, ^{99m}Tc-PYP, ^{123}I-BMIPP and ^{123}I-MIBG myocardial SPECT. ***Methods:*** We examined 7 patients with Takotsubo cardiomyopathy and 7 with AMI at the time of emergency admission (acute phase), and 2–14 days (subacute phase), one month (chronic phase), and 3 months (chronic II phase) after the attack. The left ventricle was divided into nine regions on echocardiograms and SPECT images, and the degree of abnormalities in each region was scored according to five grades from normal (0) to severely abnormal (4). ***Results:*** Coronary angiography showed the absence of stenotic regions in patients with Takotsubo cardiomyopathy, and severely stenotic and/or occlusive lesions in patients with AMI. The total ST segment elevation on electrocardiograms (mm) was 7.8 ± 3.7 in those with Takotsubo cardiomyopathy, and 7.3 ± 3.9 in patients with AMI. Abnormal wall motion scores on echocardiograms were 14.2 ± 4.6, 4.7 ± 4.0, 1.7 ± 2.0 and 0.5 ± 0.4 during the acute, subacute, chronic and chronic II phases, respectively, in patients with Takotsubo cardiomyopathy, and 14.0 ± 4.3, 11.4 ± 3.9, 8.8 ± 3.6 and 5.2 ± 4.8 in those with AMI. Abnormal myocardial perfusion scores on ^{99m}Tc-tetrofosmin images were 11.8 ± 3.5, 3.2 ± 3.0, 0.5 ± 1.2 and 0.2 ± 0.4 during the acute, subacute, chronic and chronic II phases, in patients with Takotsubo cardiomyopathy, and 16.2 ± 4.3, 13.9 ± 4.6, 7.9 ± 4.6 and 5.0 ± 4.5, respectively, in those with AMI. Abnormal myocardial fatty acid scores on ^{123}I-BMIPP images were 12.6 ± 3.7, 6.8 ± 3.2 and 0.4 ± 0.6 during the subacute, chronic and chronic II phases, respectively, in patients with Takotsubo cardiomyopathy, and 16.5 ± 5.1, 14.7 ± 4.8 and 7.5 ± 4.5 in those with AMI. Abnormal myocardial sympathetic nerve function scores on ^{123}I-MIBG images were 14.8 ± 4.0, 8.8 ± 4.0 and 0.4 ± 0.6 during the subacute, chronic, chronic II phases, respectively, in patients with Takotsubo cardiomyopathy, and 18.6 ± 6.5, 16.8 ± 6.8 and 12.9 ± 5.2 in those with AMI. Myocardial ^{99m}Tc-PYP uptake was abnormal not only in patients with AMI but also in those with Takotsubo cardiomyopathy during the acute phase. ***Conclusions:*** Takotsubo cardiomyopathy might represent a stunned myocardium caused by a disturbance of the coronary microcirculation.

Key words: Takotsubo cardiomyopathy, transient left ventricular apical ballooning, ^{99m}Tc-tetrofosmin, ^{123}I-BMIPP, ^{123}I-MIBG

INTRODUCTION

Takotsubo cardiomyopathy (transient left ventricular apical ballooning) is a heart syndrome with an acute onset defined in Japan by chest symptoms, ST segment elevation on electrocardiograms, transient balloon-like asynergy in the apical regions with hyperkinesis in the basal

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Table 1-a Clinical characteristics of patients with Takotsubo cardiomyopathy

Case No.	Gender/ Age	Underlying disorder	Trigger event	Symptoms	ECG ST elevation or Negative T	Level of CK-MB (~25 IU/*l*)	Ejection Fraction (%) (acute/chronic)	Level of Norepinephrine (~0.31 ng/m*l*)	IVST/ PWT (7~11 mm)
1	F/70	None	None	Dyspnea Chest discomfort	II, III, aV_F, $V_{2–5}$	17	49→67	0.61	10/10
2	F/83	None	Emotional stress (+) Lumbago	Chest oppression	II, III, aV_F, $V_{1–5}$	69	40→76	0.30	10/9
3	F/57	None	None	Chest pain	aV_L, $V_{1–5}$	27	38→68	0.38	8/8
4	M/65	Hypertension	Emotional stress (+) Traffic accident	Dyspnea Chest oppression	I, II, III, aV_L, V_{2-6}	15	44→72	1.92	11/8
5	F/78	Hypertension Hyperlipidemia	Emotional stress (+) Relation's death	Dyspnea Chest discomfort	II, III, aV_L, $V_{2–6}$	52	51→80	0.76	9/10
6	M/67	Hypertension Diabetes mellitus	Emotional stress (+) Dispute	Dyspnea Chest discomfort	II, III, aV_R, $V_{1–6}$	23	43→70	0.36	12/10
7	F/68	Hypertension Hyperlipidemia	Emotional stress (+) Relation's death	Chest oppression	II, III, aV_L, $V_{2–6}$	16	46→72	0.24	10/10

Table 1-b Clinical characteristics of patients with AMI

Case No.	Gender/ Age	Underlying disorder	Trigger event	Symptoms	ECG ST elevation or Negative T	Level of CK-MB (~25 IU/*l*)	Ejection Fraction (%) (acute/chronic)	Level of Norepinephrine (~0.31 ng/m*l*)	IVST/ PWT (7~11 mm)
1	M/72	Hypertension Hyperlipidemia	Playing golf	Chest pain	II, III, aV_F, $V_{2–5}$	278	46→53	0.41	10/9
2	M/81	Hypertension	None	Chest oppression	II, III, aV_F, $V_{2–5}$	425	29→39	1.16	11/10
3	F/78	Hypertension Diabetes mellitus	Taking a bath	Chest pain	III, aV_F, $V_{3–6}$	169	49→60	0.47	12/10
4	M/57	Hypertension Hyperlipidemia	None	Chest oppression Dyspnea	III, aV_F , $V_{3–6}$	313	34→41	0.83	11/8
5	F/65	None	None	Chest discomfort Dyspnea	II, III, aV_F, $V_{2–6}$	431	41→55	0.79	8/8
6	M/69	Hypertension Diabetes mellitus	None	Dyspnea	II, III, aV_F, $V_{4–6}$	141	52→64	0.51	11/11
7	M/72	Hypertension	Drinking	Chest oppression	II, III, aV_F, $V_{3–6}$	446	33→48	1.24	9/11

regions on left ventriculography, minimal myocardial enzymatic release and no significant luminal narrowing of the coronary arteries.[1–5] Left ventriculography in this syndrome reveals the shape of a Takotsubo, which is a unique Japanese fishing pot with a round bottom and narrow neck that is used for trapping octopus (octopus is "tako," and pot is "tsubo" in Japanese). Patients with Takotsubo cardiomyopathy are usually misdiagnosed as having acute myocardial infarction (AMI). Some reports have documented this syndrome, but its causative mechanism remains unknown.[1–5] We previously compared Takotsubo cardiomyopathy with AMI using ^{99m}Tc-tetrofosmin (Nihon Medi-Physics Co., Nishinomiya, Japan) myocardial single photon emission computed tomography (SPECT) which can image myocardial blood flow.[6,7] The results of that study indicated that Takotsubo cardiomyopathy might represent a stunned myocardium caused by a disturbance of the coronary microcirculation.[8] The present study evaluates Takotsubo cardiomyopathy from the perspective of myocardial perfusion, ischemic injury, fatty acid metabolism, and sympathetic nervous function using ^{99m}Tc-tetrofosmin, ^{99m}Tc-pyrophosphate (PYP; Daiichi Radioisotope Laboratories, Tokyo, Japan),[9,10] ^{123}I-15-(*p*-iodophenyl)-3-*R*,*S*-methylpentadecanoic acid (^{123}I-BMIPP; Nihon Medi-Physics Co., Nishinomiya, Japan)[11,12] and ^{123}I-metaiodobenzylguanidine (MIBG; Daiichi Radioisotope Laboratories, Tokyo, Japan).[13,14]

SUBJECTS

We examined 1,023 serial patients with suspected acute coronary syndrome and 15 with Takotsubo cardiomyopathy who satisfied the following criteria.

1) Symptoms that resembled those of acute myocardial infarction.

2) Electrocardiograms showing ST segment elevation or negative T waves in multiple leads.

3) Apical ballooning akinesis and basal hyperkinesis on left ventriculography and two-dimensional echocardiography during the acute phase.

4) Absence of organic stenotic regions in the epicardial coronary arteries, and spasms of epicardial coronary arteries ruled out by ergonovine and/or acetylcholine loading tests.

5) Absence of underlying diseases causing apical ballooning akinesis and basal hyperkinesis of the left ventricle such as multiple coronary arterial spasms,[4,15] subarachnoid hemorrhage or other cerebrovascular disorders,[16] pheochromocytoma,[17] and Guillain-Barré syndrome.[18]

We also included 7 patients (5 females and 2 males; mean age, 63.1 ± 7.1 years) from whom we could obtain complete serial SPECT images. Historical review revealed hypertension in 4 patients, hyperlipidemia in 3 and hepatic cirrhosis in one. Each of the 5 patients had emotional or physical stress that was considered to have triggered the Takotsubo cardiomyopathy as follows: death of a relative, a dispute, severe lumbago, a traffic accident as well as endoscopic retrograde and balloon occluded-retrograde transvenous obliteration. We were unable to identify any triggers in the other 2 patients (Table 1-a).

We also examined seven patients (2 females and 5 males; mean age, 68.3 ± 9.5 years) with acute myocardial infarction who satisfied the following criteria:

1) No history of myocardial infarction.

2) Coronary angiography and ^{99m}Tc-tetrofosmin myocardial SPECT performed within six hours after onset.

3) Total and/or subtotal occlusion of the proximal segment of the left anterior descending artery with no other stenotic regions on coronary angiography.

4) Hypoplastic right coronary artery, dominant left anterior descending artery and inferior wall perfused by the left anterior descending artery.

5) Apical ballooning and basal hyperkinesis, like Takotsubo cardiomyopathy, on left ventriculography and two-dimensional echocardiography during the acute phase.

6) Reperfusion after percutaneous transluminal coronary angioplasty without complications.

7) No restenosis during the chronic phase.

8) Complete serial SPECT images were available.

Although there were many patients suspected of having acute coronary syndrome, only a few of them met all of the above criteria. Historical review revealed hypertension in 6 patients, hyperlipidemia in 2 and diabetes mellitus in 2. None of the 7 patients had any apparent emotional or physical stress that was considered to be a potential trigger of AMI (Table 1-b).

All patients enrolled in this study provided written informed consent to participate in all necessary procedures.

METHODS

Protocol

Electrocardiography, blood tests, ^{99m}Tc-tetrofosmin myocardial SPECT, two-dimensional echocardiography, coronary angiography, left ventriculography and ^{99m}Tc-PYP myocardial SPECT were performed sequentially upon admission (acute phase). We also performed ^{99m}Tc-tetrofosmin, ^{123}I-BMIPP and ^{123}I-MIBG myocardial SPECT and two-dimensional echocardiography at 2–14 days (subacute phase), one month (chronic phase) and, three months (chronic phase II) after the attack, as well as left ventriculography during the acute and chronic phases. We performed right ventriculography during the acute and chronic phases, and contrast echocardiography two or three days after the attack in 5 patients with Takotsubo cardiomyopathy.

All patients were treated with an angiotensin converting enzyme inhibitor (Imidapril 5–10 mg/day) and a potassium channel opener (Nicorandil 30 mg/day). Patients with acute myocardial infarction also received aspirin (81 mg/day) and ticlopidin (100 mg/day).

Blood tests

We measured the MB fraction of creatine phosphokinase (CK-MB) and the plasma norepinephrine concentration every 6 hours starting immediately after admission until 48 hours after the attack.

^{99m}Tc-tetrofosmin myocardial SPECT

We performed emergency ^{99m}Tc-tetrofosmin myocardial SPECT immediately before coronary angiography, and during the subacute and chronic phases. The patients were intravenously injected with 740 MBq of ^{99m}Tc-tetrofosmin. SPECT images were acquired starting from 10 minutes thereafter using a digital gamma camera 901A (Toshiba Co., Tokyo, Japan) to which a low energy, high-resolution, parallel-hole collimator was attached. Data were obtained from a 64 × 64 matrix in 32 directions, namely every 6° between a left posterior oblique angle of 45° and a right anterior oblique angle of 45°, and within 30 seconds per direction. The data were collected in an online nuclear medicine data processor, GMS550U (Toshiba Co., Tokyo, Japan), and the original images were reconstituted by smoothing at 5 points. Tomographic images along the vertical long, horizontal long and short axes were created using a Shepp & Logan filter. The threshold level was 20% and absorption was not corrected. The SPECT images of the left ventricle were divided into 9 semi-quantifiable segments. The short-axis slices were separated into four segments at the basal and mid-ventricular levels and the apical portion of one segment was evaluated using vertical long-axis slices. Each segment was visually graded by assigning scores between 0 and 4 (0, normal; 1, mildly; 2, moderately and 3, obviously reduced uptake; 4, absent) by three experienced

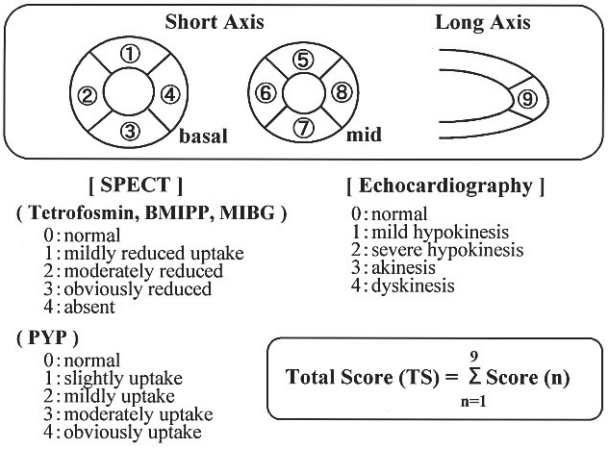


Fig. 1 Schematic representation of left ventricular segmentation. The left ventricle was divided into nine segments on two-dimensional echocardiograms, and on ^{99m}Tc-tetrofosmin, ^{99m}Tc-PYP, ^{123}I-BMIPP and ^{123}I-MIBG myocardial SPECT. Individual segments on two-dimensional echocardiograms and SPECT images were visually scored according to a five point grading system. The sum of each score was defined as the total score (TS), reflecting the severity of impaired left ventricular wall motion. Each segment on SPECT images was visually scored according to a five point grading system. The sum of each score was defined as the total score (TS), reflecting the severities of myocardial perfusion, injury, fatty acid metabolism and sympathetic nerve function impairments.

cardiologists who were blinded to other data from the patients. Differences of opinion were resolved by consensus. The sum of each score was defined as the total score (TS), reflecting the severity of impaired myocardial perfusion (Fig. 1).

Two-dimensional echocardiography

We performed two-dimensional echocardiography in all patients during the acute, subacute and chronic phases using a Sonos 5500 device (Hewlett-Packard, CA, USA). Tomographic images of the left ventricle obtained from short axial images of the sternal left edge and long axial images of the apex of the heart were divided into 9 segments. Each segment was visually graded using scores between 0 and 4 (0, normal; 1, mild hypokinesis; 2, moderate hypokinesis; 3, akinesis; 4, dyskinesis) in a blinded manner by three experienced cardiologists. Differences of opinion were resolved by consensus. The sum of each score was defined as the total score (TS), reflecting the severity of impaired left ventricular wall motion (Fig. 1).

Coronary angiography

All patients underwent coronary arteriography during the acute phase. Spasms of the epicardial coronary arteries were ruled out in patients with Takotsubo cardiomyopathy by ergonovine and/or acetylcholine loading tests during the subacute or chronic phases. Doses of 40 or 60 μg of ergonovine and of 50 or 100 μg of acetylcholine were injected within 30 seconds into the right and left coronary arteries, respectively. We ruled out restenosis during the chronic phase in patients with acute coronary syndrome.

Ventriculography

All patients underwent left ventriculography during the acute and chronic phases, and the ejection fraction of the left ventricle was calculated by the Simpson method. Four patients with Takotsubo cardiomyopathy also underwent right ventriculography during the acute and chronic phases.

^{99m}Tc-PYP myocardial SPECT

After ventriculography, we intravenously injected 370 MBq of ^{99m}Tc-PYP into all patients and obtained ^{99m}Tc-PYP SPECT images 2 hours later. The ^{99m}Tc-PYP imaging conditions were the same as those for ^{99m}Tc-tetrofosmin. The SPECT image of the left ventricle was divided into 9 regions (Fig. 1), and uptake was graded in each of them as 0, normal; 1, slight, 2 mild; 3, moderate and 4, marked. The sum of each score was defined as the total score (TS), reflecting the severity of myocardial ischemic injury due to Ca^{2+} overload.

^{123}I-BMIPP myocardial SPECT

Patients received an intravenous injection of ^{123}I-BMIPP (370 MBq) and we obtained images 15 minutes latter using a collimator exclusively for ^{123}I. The imaging conditions were the same as for ^{99m}Tc-tetrofosmin, except that the time spent for one direction was changed to 30 seconds. The SPECT image of the left ventricle was divided into 9 regions (Fig. 1), and the degree of accumulation in each region was expressed according to the 5 grades as described above. The sum of each score was defined as the total score (TS), reflecting the severity of impaired myocardial fatty acid metabolism.

^{123}I-MIBG myocardial SPECT

Patients received an intravenous injection of ^{123}I-MIBG (370 MBq) and 4 hours later we obtained images using a collimator exclusively for ^{123}I. The imaging conditions were the same as those for ^{123}I-BMIPP. The SPECT image of the left ventricle was divided into 9 regions (Fig. 1), and the degree of accumulation in each region was expressed according to the 5 grades described above. The sum of each score was defined as TS, reflecting the severity of impaired myocardial sympathetic nerve function.

Contrast echocardiography

Three patients with Takotsubo cardiomyopathy underwent contrast echocardiography at two to three days after the attack. And four with acute myocardial infarction also underwent contrast echocardiography during the sub-

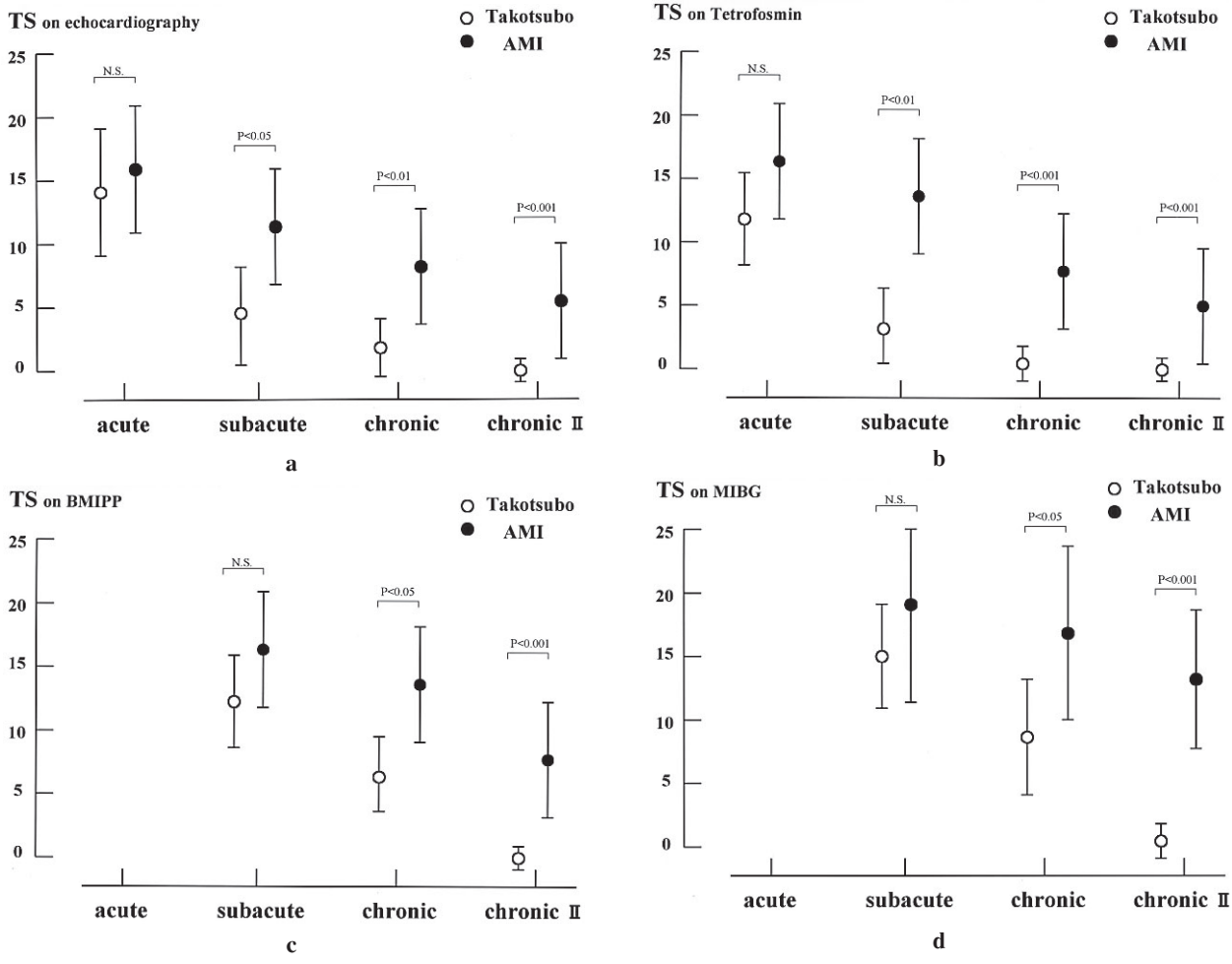


Fig. 2 a: Serial changes in impaired wall motion score (total score: TS) on two-dimensional echocardiogram. b: Serial changes in impaired myocardial perfusion score (total score: TS) on ^{99m}Tc-tetrofosmin images. c: Serial changes in impaired myocardial fatty acid metabolism score (total score: TS) on ^{123}I-BMIPP images. d: Serial changes in impaired myocardial sympathetic nerve function score (total score: TS) on ^{123}I-MIBG images.

acute phase. We obtained transthoracic two-dimensional echocardiographic images using a Sonos 5500 device (Hewlett-Packard, CA, USA). The contrast agent was Levovist™ (Shering, AG), which is composed of micro bubbles containing galactose (mean diameter 1–2 μm). Powdered Levovist™ was reconstituted by adding 7 m*l* of sterile water to achieve a final concentration of 300 mg/m*l*. An intravenous infusion of Levovist™ was injected at a rate of 1 m*l*/second. Contrast enhanced images were obtained using harmonic power-Doppler imaging in intermittent mode at each pulse interval of four cardiac cycles with the ultrasound transmission gated to the T wave of the electrocardiogram. The dynamic range of this system is 40 dB. The mechanical index was set as high as possible to increase micro bubble destruction. Transmitted power was adjusted to produce a mechanical index of 1・6. Ultrasound system gains were optimized at the beginning of the study and held as contrast for subsequent image acquisitions. The filter threshold was optimized to reduce the appearance of any color over the myocardium before the contrast injection.

Statistical processing

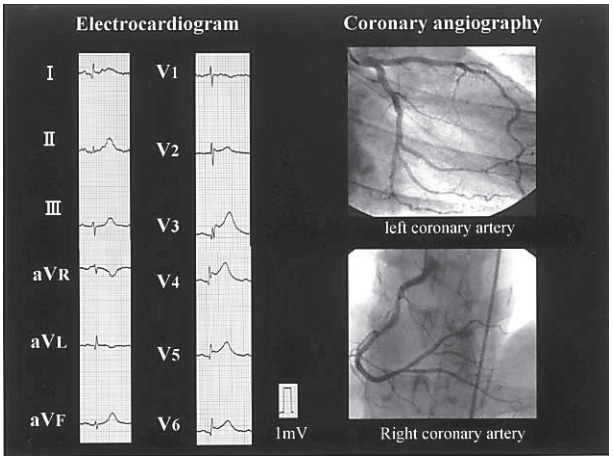
Values are expressed as means ± standard deviation. The ANOVA F test was used to evaluate differences between mean values. A hazard rate (p) of 0.05 was considered statistically significant.

RESULTS

1) The total ST segment elevation on electrocardiograms (mm) was 7.8 ± 3.7 in patients with Takotsubo cardiomyopathy and 7.3 ± 3.9 in those with acute myocardial infarction (N.S.).

2) The maximal value of CK-MB (normal; ~ 25 IU/*l*) was 32.3 ± 22.2 in patients with Takotsubo cardiomyopathy and 372.7 ± 80.7 in those with AMI ($p < 0.001$).

3) The value of plasma norepinephrine (normal;



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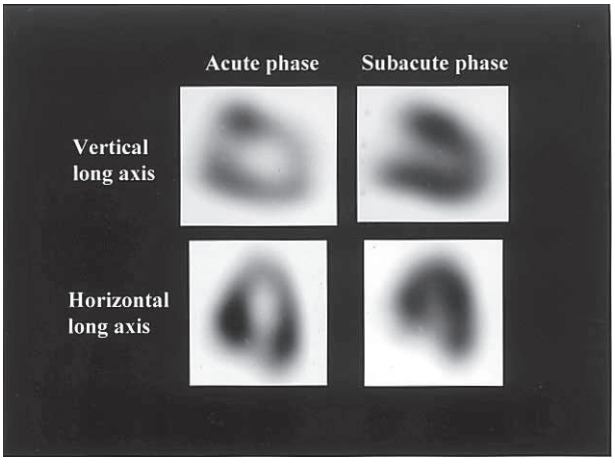

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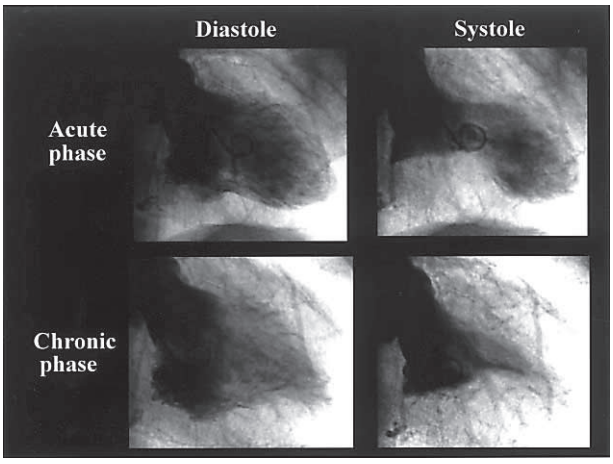

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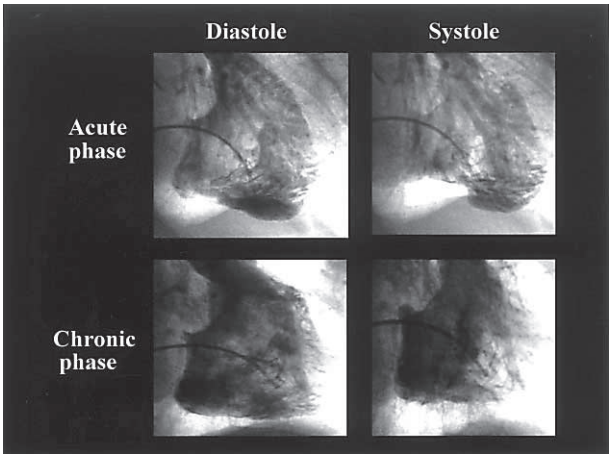

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~ 0.31 ng/m*l*) was 0.65 ± 0.59 in patients with Takotsubo cardiomyopathy and 0.77 ± 0.33 in those with AMI (Table 1-a, b). There was no significant difference in wall thickness between the Takotsubo cardiomyopathy group and the AMI group.

4) The values of intraventricular septal thickness (IVST) (normal; 7–11 mm) and posterior wall thickness (PWT) (normal; 7–11 mm) were 10.0 ± 1.3 and 9.3 ± 1.0, respectively, in patients with Takotsubo cardiomyopathy. Those values were 10.3 ± 1.4 and 9.6 ± 1.3, respectively, in patients with AMI (Table 1-a, b). There was no significant difference in wall thickness between the Takotsubo cardiomyopathy group and the AMI group.

5) The TS values on two-dimensional echocardiography in patients with Takotsubo cardiomyopathy were 14.2 ± 4.6, 4.7 ± 4.0, 1.7 ± 2.0 and 0.5 ± 0.4 during the acute, subacute, chronic and chronic II phases, respectively. In patients with AMI, these values were 14.0 ± 4.3, 11.4 ± 3.9, 8.8 ± 3.6 and 5.2 ± 4.8, respectively (Fig. 2-a).

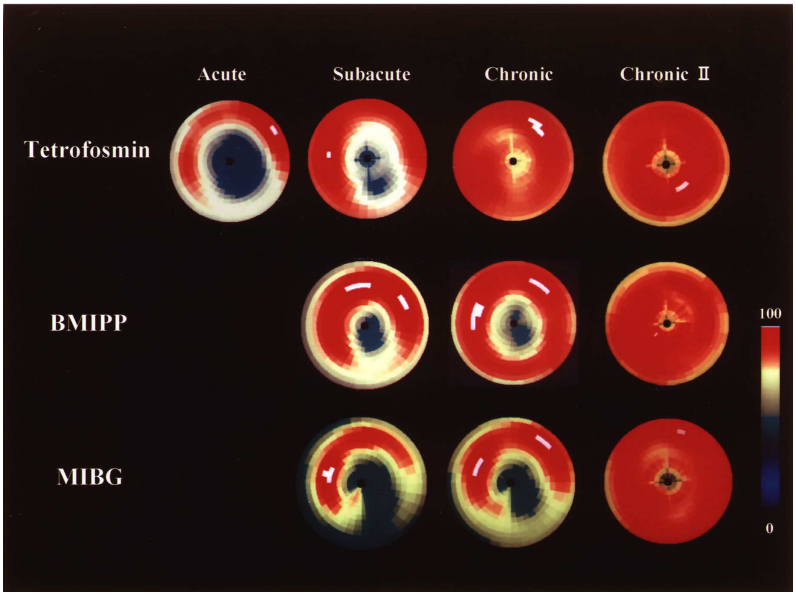
6) The TS values on ^{99m}Tc-tetrofosmin myocardial SPECT in patients with Takotsubo cardiomyopathy were 11.8 ± 3.5, 3.2 ± 3.0, 0.5 ± 1.2, and 0.2 ± 0.4, during the acute, subacute, chronic and chronic II phases, and during, respectively. In patients with AMI, these values were 16.2 ± 4.3, 13.9 ± 4.6, 7.9 ± 4.6, and 5.0 ± 4.5, respectively (Fig. 2-b).

7) The TS values on ^{123}I-BMIPP myocardial SPECT in patients with Takotsubo cardiomyopathy were 12.6 ± 3.7, 6.8 ± 3.2 and 0.4 ± 0.6 during the subacute and chronic phases and chronic II phases, respectively. In patients with AMI, these values were 16.5 ± 5.1, 14.7 ± 4.8 and 7.5 ± 4.5 during the subacute, chronic and chronic II phases (Fig. 2-c).

8) The TS values on ^{123}I-MIBG myocardial SPECT in patients with Takotsubo cardiomyopathy were 14.8 ± 4.0, 8.8 ± 4.0 and 0.6 ± 0.5, respectively. In patients with AMI, the respective values were 18.6 ± 6.5, 16.8 ± 6.8 and 12.9 ± 5.2 (Fig. 2-d).

9) The numbers of segments in which ^{99m}Tc-tetrofosmin uptake was absent during the acute phase were 0.6 ± 0.7 and 3.8 ± 3.0 in patients with Takotsubo cardiomyopathy and AMI, respectively ($p < 0.01$).

10) The TS values on ^{99m}Tc-PYP myocardial SPECT were 3.2 ± 3.0 and 11.8 ± 3.5 in patients with Takotsubo



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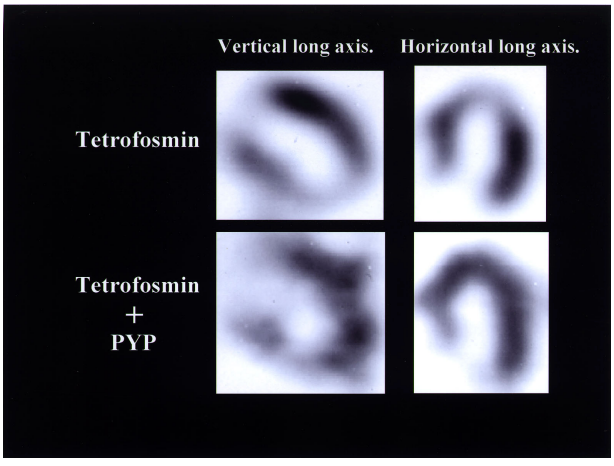

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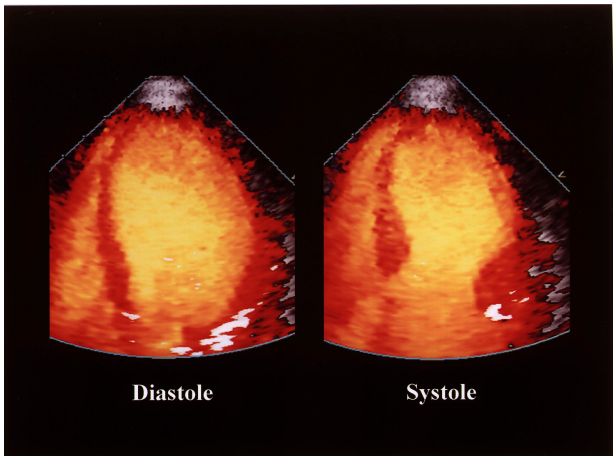

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Fig. 3 Case presentation (Takotsubo cardiomyopathy). a: Electrocardiography and Coronary angiography. Upon admission, electrocardiography showed elevated ST segments in leads I, aV_L and V_{2-6}, but stenotic lesions were absent on coronary angiography. b: ^{99m}Tc-tetrofosmin myocardial SPECT. Myocardial SPECT with ^{99m}Tc-tetrofosmin showed severely reduced, but not absent, uptake from the mid-portion to the apical area. These findings normalized during the chronic phase. c: Left ventriculography. Apical ballooning akinesis and basal hyperkinesis were observed, and these dysfunctions normalized during the chronic phase. d: Right ventriculography. Apical ballooning akinesis and basal hyperkinesis were observed, and these dysfunctions normalized during the chronic phase. e: Serial changes in ^{99m}Tc-tetrofosmin, ^{123}I-BMIPP and ^{123}I-MIBG images (Bull's-eye plot). Impaired myocardial perfusion on ^{99m}Tc-tetrofosmin images normalized during the chronic phase, impaired myocardial fatty acid metabolism on ^{123}I-BMIPP and sympathetic nerve function on ^{123}I-MIBG normalized during the chronic II phase. f: ^{99m}Tc-PYP myocardial SPECT. Regions in which ^{99m}Tc-tetrofosmin images showed severely reduced uptake during the acute phase in patients with Takotsubo cardiomyopathy were found to be positive for ^{99m}Tc-PYP myocardial uptake. g: Contrast echocardiography. Myocardial perfusion was maintained in ballooning apical regions in patients with Takotsubo cardiomyopathy even during the early subacute phase.

cardiomyopathy and AMI, respectively. In regions where ^{99m}Tc-tetrofosmin images showed severely reduced uptake or no uptake during the acute phase in both patient groups, ^{99m}Tc-PYP was taken up by the myocardium.

11) Ejection fraction values on left ventriculography were 42.3 ± 4.0% in patients with Takotsubo cardiomyopathy, 39.7 ± 8.4% in those with AMI during the acute phase (N.S.), and 70.6 ± 6.0% and 52.8 ± 9.0%, respectively, during the chronic phase ($p < 0.01$).

12) Right ventriculography was performed in five patients with Takotsubo cardiomyopathy, all of whom showed apical ballooning akinesis and basal hyperkinesis during the acute phase. This abnormal wall motion improved during the chronic phase.

13) Contrast echocardiography revealed myocardial perfusion in the ballooning apical region in three patients with Takotsubo cardiomyopathy even during the early subacute phase, and severely reduced myocardial perfusion in the apical region in three patients with AMI during the subacute phase.

Case Presentation

Takotsubo cardiomyopathy

Electrocardiography revealed elevated ST segments in leads I, II, aV_L and V_{2-6}, but coronary angiography revealed no stenotic regions (Fig. 3-a). ^{99m}Tc-tetrofosmin myocardial SPECT showed that uptake, though not absent, was severely reduced from the mid-portion to the apical area upon admission. These findings normalize during the subacute phase (Fig. 3-b). Left and right ventriculography showed apical ballooning akinesis and basal hyperkinesis during the acute phase, which normalized during the chronic phase (Fig. 3-c, d). Impaired myocardial perfusion on ^{99m}Tc-tetrofosmin images (Bull's-eye plot) normalized during the chronic phase, as did impaired myocardial fatty acid metabolism on ^{123}I-BMIPP and sympathetic nerve function on ^{123}I-MIBG during the chronic II phase (Fig. 3-e). The myocardium absorbed ^{99m}Tc-PYP in apical ballooning regions where uptake of ^{99m}Tc-tetrofosmin was reduced (Fig. 3-f). Contrast echocardiography revealed myocardial perfusion in the ballooning apical region even during the early subacute phase (Fig. 3-g).

DISCUSSION

Several reports have noted transient left ventricular apical ballooning akinesis and basal hyperkinesis without coronary stenosis to be associated with Takotsubo cardiomyopathy.[1–5] These reports also suggested that multiple spasms of the epicardial coronary arteries, microcirculatory disturbances or myocardial damage induced by catecholamines could be causative mechanisms. However, this has remained a matter of speculation. The present study assessed Takotsubo cardiomyopathy using blood tests, echocardiography, coronary angiography, ventriculography and myocardial SPECT imagings with ^{99m}Tc-tetrofosmin, ^{99m}Tc-PYP, ^{123}I-BMIPP and ^{123}I-MIBG.

^{99m}Tc-tetrofosmin can easily be labeled in the hospital, and myocardial perfusion images can be visualized on ^{99m}Tc-tetrofosmin SPECT.[6,7] In addition, ^{99m}Tc-tetrofosmin myocardial SPECT can be performed even during the acute phase in patients with acute myocardial infarction. Therefore, this procedure is extensively applied to diagnosing ischemic heart diseases and to evaluating pathological conditions.[19] Since ^{99m}Tc-PYP binds to calcium, hydroxyapatite crystals, in the necrotic myocardium, it can facilitate diagnosing and quantifying acute-phase myocardial infarction in the clinical setting.[9,10] However, several recent reports have indicated that ^{99m}Tc-PYP is taken up by the myocardium in patients with unstable angina. Furthermore, ^{99m}Tc-PYP is taken up by viable but severely damaged myocardial cells. Therefore, ^{99m}Tc-PYP uptake is also considered to be an indicator of myocardial ischemic injury without infarction.[20,21] Under aerobic conditions and at rest while fasting, 60% to 90% of the energy requirement of the myocardium is supplied by fatty acid metabolism. However, under hypoxic or ischemic conditions, fatty acid metabolism, which requires a large amount of oxygen, is suppressed and replaced by glucose metabolism, which requires less oxygen. Therefore, myocardial fatty acid metabolism imaging can reflect myocardial ischemia. The radioiodinated branched chain fatty acid ^{123}I-BMIPP was developed to investigate myocardial fatty acid metabolism using SPECT imaging. This procedure is also extensively applied to diagnosing ischemic heart diseases and to evaluating pathological conditions.[12,22] Impaired myocardial fatty acid metabolism on ^{123}I-BMIPP images recovers after myocardial perfusion improves on ^{201}Tl images in patients with a stunned myocardium. Thus, the discrepancies between ^{123}I-BMIPP and ^{201}Tl uptake, reduced ^{123}I-BMIPP and maintained ^{201}Tl uptake, suggest a stunned myocardium.[23] On the other hand, heart function is regulated by the neurohormonal system, especially the sympathetic nervous system. Myocardial sympathetic nerve function is easily suppressed under ischemic conditions. Images of myocardial nerve function can reflect myocardial ischemia. The radioiodinated analog for norepinephrine, ^{123}I-MIBG, can image myocardial sympathetic nerve function using SPECT.[13,14] This procedure is also routinely applied to diagnosing ischemic heart diseases and to evaluating pathological conditions.[24] The myocardial sympathetic nervous system impairment seen on ^{123}I-MIBG images recovers later than the improvement in myocardial perfusion on ^{201}Tl images in patients with a stunned myocardium. Thus, the discrepancies between myocardial ^{123}I-MIBG and ^{201}Tl uptake, reduced ^{123}I-MIBG and maintained ^{201}Tl uptake, suggest a stunned myocardium.[25]

The present study as well as others demonstrated sudden onset with chest symptoms, elevated ST segments on

electrocardiograms and severely reduced left ventricular wall motion in patients with Takotsubo cardiomyopathy. The degree of ST segment elevation and reduced wall motion did not differ significantly between the two groups. Furthermore, during the acute phase, reduced myocardial ^{99m}Tc-tetrofosmin uptake and abnormal ^{99m}Tc-PYP uptake were observed not only in patients with AMI but also in those with Takotsubo cardiomyopathy. Therefore, severe myocardial ischemia is closely related to the causative mechanism of Takotsubo cardiomyopathy.

Reduced left ventricular wall motion on two-dimensional echocardiography and myocardial perfusion on ^{99m}Tc-tetrofosmin images and contrast echocardiography showed moderate to complete recovery at two weeks after the attack, and had normalized at one month after the attack in patients with Takotsubo cardiomyopathy. In patients with AMI, these parameters showed no or mild improvement at two weeks after the attack, mild to moderate improvement at one month after the attack, and were moderately improved at three months after the attack. From the viewpoints of the recovered wall motion and myocardial perfusion, AMI was considered to represent a stunned myocardium,[15] and Takotsubo cardiomyopathy might also be regarded as a type of stunned myocardium.

We also assessed myocardial fatty acid metabolism and sympathetic nerve function using ^{123}I-BMIPP and ^{123}I-MIBG myocardial SPECT. These findings deteriorated not only in AMI but also in Takotsubo cardiomyopathy. The degree of damage ranged from moderate to severe at two weeks after the attack, but had almost normalized at one month after the attack in patients with Takotsubo cardiomyopathy. In patients with AMI, damage was severe at two weeks after the attack and did not improve, and improved mildly at one month after the attack, and moderately at three months after the attack. Myocardial fatty acid metabolism and sympathetic nerve function improved after myocardial perfusion and wall motion recovery. Thus, the serial changes in myocardial fatty acid metabolism and sympathetic nerve function were very similar in the two groups, even though a difference was noted at the time of recovery. Considering the results of examinations of impaired myocardial fatty acid metabolism and myocardial sympathetic nerve function, Takotsubo cardiomyopathy might also be regarded as a type of stunned myocardium.

Spasm was not evident in the epicardial coronary arteries of patients with Takotsubo cardiomyopathy. Thus, multiple spasms of the epicardial coronary arteries were not considered relevant, whereas impaired coronary microcirculation[26] seemed to be a causative mechanism of Takotsubo cardiomyopathy. The epicardial coronary arteries ramify into a network of small vessels, such as the subepicardial artery (200 μm), intramuscular arterioles (100–30 μm), precapillaries (20–10 μm), capillaries (8–5 μm), and venules.[27] Biopsy pathology in Takotsubo cardiomyopathy has sometimes revealed injury to focal myocytes, but not to transmural myocytes, and such injury was not induced by epicardial coronary artery occlusion.[1] When microspheres with a diameter of 15 μm are injected into the coronary artery, multiple focal ischemic myocyte injuries with long and short axes of 300 and 100 μm appear.[27,28] In Takotsubo cardiomyopathy, coronary angiography revealed patency during the acute phase with ST elevation on electrocardiograms and akinesis on left ventriculography, and contrast echocardiography revealed myocardial perfusion in the ballooning regions at two to three days after the attack. When microspheres with a diameter of 15–50 μm are injected into the coronary artery, coronary blood flow does not adversely decrease even while myocardial ischemia is induced.[29] That the coronary artery is patent during the acute phase in patients with Takotsubo cardiomyopathy does not contradict the notion that this condition is induced by impaired coronary microcirculation. In patients with coronary microvascular spasm, epicardial coronary flow remains patent during the acute phase with ST segment elevation on electrocardiograms.[30]

Coronary microvascular spasm[30] or coronary microvascular diastolic functional abnormalities[26] are considered a cause of impaired coronary microcirculation. However, when myocardial ischemia is caused by impaired coronary microvascular diastolic functional abnormalities, electrocardiography does not show elevated ST segments, and left ventricular wall motion is not as severely reduced as it is in AMI. Furthermore, contrast echocardiography showed myocardial perfusion even at a few days after the attack. Therefore, microvascular spasm might be a mechanism of myocardial ischemia in patients with Takotsubo cardiomyopathy.

Many of the patients developed Takotsubo cardiomyopathy after enduring psychological stress such as an accident involving a family member, the death of a loved one, a quarrel or excessive excitation. Under such stressful situations, excess norepinephrine might be secreted from the sympathetic nervous system, which might provoke microvascular spasm via α2 receptors.[31] Sympathetic nerves are also distributed to smaller vessels as intramuscular arterioles, but parasympathetic nerves are only distributed to the epicardial and subepicardial arteries.[32] Therefore, the influence of the sympathetic nerves extends to the coronary microcirculation. Electrocardiograms of restrained pigs have shown negative T waves and/or ST segment elevation in 61%, and 13% died suddenly.[33] Myocardial ischemia is induced in humans by psychological stress, and the risk of sudden cardiac death increases with high levels of such stress.[34,35] Emotional stress in the rat transiently reduces left ventricular wall motion to assume a Takotsubo-like shape and this can be normalized by a prior adrenoceptor blockade.[36] Five of 7 of our patients were psychologically stressed at the time of the attack, which might have caused excessive secretion of catecholamines and abnormally increased

coronary microvascular tonus, namely spasm. However, no definite psychological stress was evident in the other 2 patients. An imbalance in neurohumoral factors or excessive catecholamine secretion could have caused coronary microvascular spasm. The plasma norepinephrine concentration was increased in five of seven patients in the present study. Three of our patients also had apical akinesis and basal hyperkinesis of the right ventricle. These phenomena suggested that an imbalance in neurohumoral factors and/or excessive catecholamine secretion in not only the left but also in the right ventricle might be a causative mechanism of Takotsubo cardiomyopathy.

A balloon-like asynergy in the apical regions and hyper contraction in the basal regions of the left ventricle have been demonstrated in Takotsubo cardiomyopathy. However, why the left ventricle assumes this specific shape remains unknown. The numbers of sympathetic nerve endings and their receptors on the myocardium differ in the left ventricle of the dog. In the apical legion of the left ventricle, the number of sympathetic nervous endings is decreased, whereas the number of receptors is increased. On the contrary, the opposite is true in the basal region of the left ventricle.[37] These disturbances might be related to the balloon-like asynergy in the apical regions and the hyperkinesis in the basal regions of the bilateral ventricles. However, the distribution of sympathetic nerve endings and their receptors in humans remains obscure.

This specific systolic form of left ventricular, apical ballooning and basal hyperkinesis, obstructed the left ventricular outflow tract. Furthermore, it was reported that the pressure gradient resulting from the outflow tract obstruction might be related to the cause of Takotsubo cardiomyopathy. Since we did not examine the pressure gradient in the left ventricular outflow tract, we cannot discuss it in detail. However, the right ventricle, which showed no significant outflow tract obstruction, revealed transient abnormal wall motion. Therefore, the primary cause of Takotsubo cardiomyopathy was not considered to be outflow tract obstruction.

The ST segments were equally elevated on electrocardiograms and abnormal wall motions were equal in the two groups during the acute phase. However, the CK values and the degree of myocardial ^{99m}Tc-PYP uptake during the acute phase were significantly lower, and the degrees of improved wall motion, myocardial fatty acid metabolism and myocardial sympathetic nerve function during the subacute and chronic phases were significantly higher in patients with Takotsubo cardiomyopathy. Myocardial damage in patients with Takotsubo cardiomyopathy was transient, as it is in the stunned myocardium.[8] During the acute phase, myocardial ^{99m}Tc-tetrofosmin uptake was severely reduced in patients with Takotsubo cardiomyopathy, but only a few segments revealed absent ^{99m}Tc-tetrofosmin uptake. The CK-MB level was much lower in patients with Takotsubo cardiomyopathy than in those with AMI. These results suggested that some myocardial perfusion remained during the acute phase in patients with Takotsubo cardiomyopathy. Such residual perfusion could preserve fundamental myocardial functions such as those of the membrane and the mitochondria, while myocardial damage is reduced and can improve during the early phase, as in the stunned myocardium.

The present study indicated that Takotsubo cardiomyopathy might be a type of stunned myocardium caused by impaired coronary microcirculation, but further studies involving more patients and basic experiments are required.

REFERENCES

1. Kawai S, Suzuki H, Yamaguchi H, Tanaka K, Sawada H, Aizawa T, et al. Ampulla cardiomyopathy (Takotsubo cardiomyopathy) —Reversible left ventricular dysfunction with ST segment elevation—. *Jpn Circ J* 2000; 64: 156–159.
2. Nyui N, Yamanaka O, Nakamura R, Sawano M, Kawai S. 'Tako-tsubo' transient ventricular dysfunction—A case report—. *Jpn Circ J* 2000; 64: 715–719.
3. Tsuchihashi K, Ueshima K, Uchida T, Ohmura N, Kimura K, Owa M, et al. Transient left ventricular apical ballooning without coronary artery stenosis: A novel heart syndrome mimicking acute myocardial infarction. *J Am Coll Cardiol* 2001; 38: 11–18.
4. Dote K, Sato H, Tateishi H, Uchida T, Ishihara M. Myocardial stunning due to simultaneous multivessel coronary spasms: a review of 5 cases. *J Cardiol* 1991; 21: 203–214.
5. Iga K, Hori K, Kitaguchi K, Matsumura T, Gen H, Tomonaga G, et al. Transient segmental asynergy of the left ventricle of patients with various clinical manifestations possibly unrelated to the coronary artery disease. *Jpn Circ J* 1991; 55: 1061–1067.
6. Tamaki N, Takahashi N, Kawamoto M, Torizuka T, Tadamura E, Yonekura Y, et al. Myocardial tomography using technetium-99m-tetrofosmin to evaluate coronary artery disease. *J Nucl Med* 1994; 35: 594–600.
7. Sugihara H, Nakagawa T, Yamashita E, Kinoshita N, Ito K, Azuma A, et al. Reverse redistribution of Tc-99m-tetrofosmin in patients with acute myocardial infarction. *Ann Nucl Med* 1999; 13: 43–47.
8. Ito K, Sugihara H, Katoh S, Azuma A, Nakagawa M. Assessment of Takotsubo (ampulla) cardiomyopathy using ^{99m}Tc-tetrofosmin myocardial SPECT—comparison with acute coronary syndrome—. *Ann Nucl Med* 2003; 17: 115–122.
9. Bonte FJ, Parkey RW, Graham KD, More J, Stokely EM. A new method for radionuclide imaging of myocardial infarction. *Radiology* 1974; 110: 473–474.
10. Jansen DE, Corbett JR, Buja M, Hansen C, Ugoline V, Parkey RW, et al. Quantification of myocardial injury produced by temporary coronary artery occlusion and reflow with technetium-99m-pyrophosphate. *Circulation* 1987; 75: 611–617.
11. Reske SN, Sauer W, Machulla HJ, Knust J, Winkler C. Metabolism of 15 (*p*-^{123}I-iodophenyl-) pentadecanoic acid in heart muscle and non cardiac tissue. *Eur J Nucl Med* 1985; 10: 228–234.

12. Ito K, Sugihara H, Kawasaki T, Katoh S, Azuma A, Nakagawa M. Dynamic change in cardiac fatty acid metabolism in the stunned human myocardium. *Ann Nucl Med* 2001; 15: 343–350.
13. Mock BH, Tuli M. Influence of specific activity on myocardial uptake of ^{123}I-MIBG in rats. *Nucl Med Commun* 1987; 9: 663–667.
14. Wieland DM, Brown LE, Rogers WL, Worthington KC, Wu JL, Clinthorone NH, et al. Myocardial imaging with a radioiodinated norepinephrine storage analog. *J Nucl Med* 1981; 22: 22–31.
15. Braunwald E, Kloner RA. The stunned myocardium: prolonged, postischemic ventricular dysfunction. *Circulation* 1982; 66: 1146–1149.
16. Ohtsuka T, Hamada M, Kodama K, Sasaki O, Suzuki M, Hara Y, et al. Neurogenic stunned myocardium. *Circulation* 2000; 101: 2122–2124.
17. Salathe M, Weiss P, Ritz R. Rapid reversible of heart failure in a patient with phaeochromocytoma and catecholamine-induced cardiomyopathy who was treated with captopril. *Br Heart J* 1992; 68: 527–528.
18. Iga K, Himura Y, Izumi C, Miyamoto T, Kijima K, Gen H, et al. Reversible left ventricular dysfunction associated with Guillain-Barré syndrome: An expression of catecholamine cardiotoxicity? *Jpn Circ J* 1995; 59: 236–240.
19. Abbott BG, Wackeres FJ. Emergency department chest pain units and the role of radionuclide imaging. *J Nucl Cardiol* 1998; 5: 73–79.
20. Olson HG, Lyons KP, Aronow WS, Stinson PJ, Kuperus J, Waters HJ. The high-risk angina patient: Identification by clinical features, hospital course, electrocardiography and technetium-99m stannous pyrophosphate scintigraphy. *Circulation* 1981; 64: 674–684.
21. Okuda K, Nohara R, Fujita M, Tamaki N, Konishi J, Sasayama S. Technetium-99m-Pyrophosphate uptake as an indicator of myocardial injury without infarct. *J Nucl Med* 1994; 35: 1366–1370.
22. Kawai Y, Tsukamoto E, Nozaki Y, Morita K, Sakurai M, Tamaki N. Significance of reduced uptake of iodinated fatty acid analogue for the evaluation of patients with acute chest pain. *J Am Coll Cardiol* 2001; 38: 1888–1894.
23. Tamaki N, Kawamoto M, Yonekura Y, Fujibayashi Y, Takahashi N, Konishi J, et al. Regional metabolic abnormality in relation to perfusion and wall motion in patients with myocardial infarction: assessment with emission tomography using an iodinated branched fatty acid analog. *J Nucl Med* 1992; 33: 659–667.
24. Stanton MS, Tuli MM, Radtke NL, Heger JJ, Miles WM, Mock BH, et al. Regional sympathetic denervation after myocardial infarction in humans detected noninvasively using I-123 metaiodobenzylguanidine. *J Am Coll Cardiol* 1989; 14: 1519–1526.
25. Sakata K, Yoshida H, Hoshino T, Kurata C. Sympathetic nerve activity in the spasm induced coronary artery region is associated with disease activity of vasospastic angina. *J Am Coll Cardiol* 1996; 28: 460–464.
26. Cannon RO, Epstein SE. Microvascular angina as a cause of chest pain with angiographically normal coronary arteries. *Am J Cardiol* 1988; 61: 1338–1343.
27. Sherf L, Ben-Shaul Y, Lieberman Y, Neufeld HN. The human coronary circulation: An electron microscopic study. *Am J Cardiol* 1977; 39: 599–607.
28. Guzman SV, Swenson E, Jones M. Intracoronary reflex. Demonstration by coronary angiography. *Circ Res* 1962; 10: 739–745.
29. Hori M, Tamai J, Kitakaze M, Iwakura K, Rotoh K, Iwai K, et al. Adenosine-induced hyperemia attenuates myocardial ischemia in coronary microembolization in dogs. *Am J Physiol* 1989; 257: 244–251.
30. Nagai H, Nakamura Y, Tanaka S, Kobayashi K. Angina pectoris associated with ST segment elevation in the absence of epicardial coronary arterial obstruction. *Angiology* 1994; 45: 391–397.
31. Berne RM. Coronary circulation. In *Handbook of Physiology. Vol. I The heart*. Berne RM et al. (eds), Bethesda; American Physiological Society, 1979: 873.
32. Hirsch EF, Broghard-Erdle AM. The innervation of the human heart. I The coronary arteries and the myocardium. *Arch Pathol* 1961; 71: 384–407.
33. Johansson G, Jonesson L, Lannek N, Blomgren L, Lindberg P, Poupa O. Severe stress-cardiopathy in pigs. *Am Heart J* 1987; 87: 451–457.
34. Leor J, Poole WK, Kloner RA. Sudden cardiac death triggered by an earthquake. *N Engl J Med* 1996; 334: 413–419.
35. Cebelin MS, Hirsch CS. Human stress cardiomyopathy: Myocardial lesions in victims of homicidal assaults without internal injuries. *Hum Path* 1980; 11: 123–132.
36. Ueyama T, Kasamutsu K, Hano T, Yamamoto K, Tsuruo Y, Nishino I. Emotional stress induced transient left ventricular hypocontraction in the rat via activation of cardiac adrenoceptors—A possible animal model of Tako-tsubo cardiomyopathy. *Circ J* 2002: 66: 712–713.
37. Murphree SS, Saffitz JE. Quantitative autoradiographic delineation of the distribution of beta-adrenergic receptors in canine and feline left ventricular myocardium. *Circ Res* 1987; 60: 568–579.