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Assessment of *Takotsubo* (ampulla) cardiomyopathy using ^{99m}Tc-tetrofosmin myocardial SPECT —Comparison with acute coronary syndrome—

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We assessed *Takotsubo* (ampulla) cardiomyopathy compared with acute coronary syndrome (ACS) using two-dimensional echocardiography and ^{99m}Tc-tetrofosmin myocardial SPECT. ***Methods:*** We examined 10 patients with *Takotsubo* cardiomyopathy and 16 with ACS at the time of emergency admission (acute phase), at three to nine days after the attack (subacute phase) and at one month after the attack (chronic phase). The left ventricle was divided into nine regions on echocardiograms and SPECT images, and the degree of abnormalities in each region was scored in five grades from normal (0) to severely abnormal (4). ***Results:*** Coronary angiography revealed total or subtotal occlusion in patients with ACS but no stenotic legions in those with *Takotsubo* cardiomyopathy. The amount of ST segment elevation (mm) was 7.9 ± 3.4 in patients with *Takotsubo* cardiomyopathy and 7.3 ± 3.7 in those with ACS (N.S.). Abnormal wall motion scores on echocardiograms were 13.8 ± 4.4, 4.4 ± 3.8 and 1.8 ± 2.3 during the acute, subacute and chronic phases in patients with *Takotsubo* cardiomyopathy, and 13.9 ± 4.0, 11.7 ± 3.7, 7.6 ± 4.2, respectively in patients with ACS. The value of MB fraction of creatine phosphokinase (IU/*l*) was 34 ± 23 in patients with *Takotsubo* cardiomyopathy and 326 ± 98 in those with ACS ($p < 0.001$). Abnormal myocardial perfusion scores on ^{99m}Tc-tetrofosmin myocardial SPECT were 11.4 ± 3.2, 3.2 ± 3.3 and 0.7 ± 1.1 during the acute, subacute and chronic phases respectively, in patients with *Takotsubo* cardiomyopathy, and 15.8 ± 4.1, 13.5 ± 4.4, 8.2 ± 4.4, respectively, in those with ACS. The numbers of myocardial segments that did not uptake ^{99m}Tc-tetrofosmin during the acute phase were 0.5 ± 0.8 and 3.6 ± 2.8 in patients with *Takotsubo* cardiomyopathy and ACS, respectively. ***Conclusion:*** Impaired coronary microcirculation might be a causative mechanism of *Takotsubo* cardiomyopathy.

Key words: *Takotsubo* cardiomyopathy, ampulla cardiomyopathy, ^{99m}Tc-tetrofosmin, microcirculation

INTRODUCTION

A HEART SYNDROME with acute onset defined by chest symptoms, elevated ST segment on electrocardiograms, transient balloon-like asynergy in the apical regions and hyperkinesis in the basal regions on left ventriculography, minimal myocardial enzymatic release and no significant luminal narrowing of the coronary artery, is named *Takotsubo* cardiomyopathy (ampulla cardiomyopathy) in Japan.[1–5] Left ventriculography of this syndrome reveals the shape of a *takotsubo*, which is a unique fishing pot with a round bottom and narrow neck that is used for trapping octopus in Japan (octopus is "tako," and pot is "tsubo" in Japanese). Patients with *Takotsubo* cardiomyopathy are usually misdiagnosed as having acute myocardial infarction. Some reports have documented this syndrome, but its causative mechanism remains unknown.[1–5] This prompted us to compare *Takotsubo*

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cardiomyopathy with acute coronary syndrome 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]

SUBJECTS

We studied ten patients (7 females and 3 males; mean age, 63.1 ± 7.1 years) with *Takotsubo* cardiomyopathy who were discovered among 573 serial patients with suspected acute coronary syndrome and who satisfied the following criteria:

1) Symptoms that resembled those of acute myocardial infarction.
2) Electrocardiogram showed elevation of ST segments or negative T wave 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 lesions in the epicardial coronary arteries and spasms of epicardial coronary arteries ruled out by ergonovine or acetylcholine loading tests.
5) Absence of underlying diseases which revealed apical ballooning akinesis and basal hyperkinesis of left ventricule such as multiple coronary arterial spasms,[4,8] subarachnoid hemorrhage or other cerebrovascular disorders,[9–11] pheochromocytoma,[12,13] Guillain-Barre syndrome.[14]

Past histories consisted of hypertension in 4 cases, hyperlipidemia in 1 case, chronic pancreatitis in 1 case, and hepatic cirrhosis in 1 case. Six patients had emotional or physical stress that was considered as a trigger event of *Takotsubo* cardiomyopathy, relation's death in 1 case, dispute in 1 case, severe lumbago in 1 case, traffic accident in 1 case, endoscopic retrograde cholangiopancreatography in 1 case and balloon occluded-retrograde transvenous obliteration in 1 case. We could not detect any trigger event in the other 4 cases (Table 1)

We also examined sixteen patients (5 females and 11 males; mean age, 68.3 ± 9.5 years) with acute coronary syndrome who satisfied the following criteria:

1) No history of myocardial infarction.
2) Coronary angiography and ^{99m}Tc-tetrofosmin myocardial SPECT could be performed within six hours after onset.
3) Total and/or subtotal occlusion of the proximal segment of the left anterior descending artery on coronary angiograms.
4) Reperfusion was obtained after percutaneous transluminal coronary angioplasty without complications.
5) No restenosis during the chronic phase.

Table 1 Clinical characteristics

Case No.	Gender/ Age	Underlying disorder	Trigger event	Symptoms	ECG ST elevation or Negative T	Level of CPK-MB (~25 IU/*l*)	Ejection fraction (%) (acute/chronic)	Level of Norepinephrine (~0.31 ng/m*l*)
1	F/72	Hypertension	Emotional stress (+) Relation's death	Chest pain	II, III, aV_F, V_{2-6}	16	45→78	Not done
2	F/73	None	None	Dyspnea	I, aV_L, V_{2-6}	24	50→68	Not done
3	M/56	Chronic pancreatitis	Emotional stress (+) Endoscopic retrograde cholangiopancreatography	Chest pain Back pain	I, II, III, aV_L, V_{2-5}	73	38→74	Not done
4	F/62	Hypertension Hyperlipidemia	Emotional stress (+) Dispute	Dyspnea	I, aV_L, V_{1-5}	20	47→71	Not done
5	F/58	Hypertension	None	Syncope Chest oppression	II, III, aV_F, V_{2-6}	16	45→69	0.42
6	M/65	Hepatic cirrhosis esophageal varix	Emotional stress (+) Balloon occluded-retrograde transvenous obliteration	Chest pain	I, II, III, aV_L, V_{2-6}	59	42→80	2.12
7	F/70	None	None	Dyspnea Chest discomfort	II, III, aV_F, V_{2-5}	17	49→67	0.61
8	F/83	None	Emotional stress (+) Lumbago	Chest oppression	II, III, aV_F, V_{1-5}	69	40→76	0.30
9	F/57	None	None	Chest pain	aV_L, V_{1-5}	27	38→68	0.38
10	M/65	Hypertension	Emotional stress (+) Traffic accident	Dyspnea Chest oppression	I, II, III, aV_L, V_{2-6}	21	44→72	1.92

METHODS

Protocol

After admission, electrocardiography, blood tests, ^{99m}Tc-tetrofosmin myocardial SPECT, two-dimensional echocardiography, coronary angiography and left ventriculography were performed during the acute phase. We also repeated ^{99m}Tc-tetrofosmin myocardial SPECT and two-dimensional echocardiography at three to nine days after the attack (subacute phase) and at one month after the attack (chronic phase), as well as left ventriculography during the subacute phase or chronic phase.

All patients were treated with an angiotensin converting enzyme inhibitor (Imidapril 5–10 mg/day) and K channel opener (Nicorandil 30 mg/day).

Blood tests

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

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 wall motion score (TWS), reflecting the severity of impaired left ventricular wall motion (Fig. 1).

^{99m}Tc-tetrofosmin myocardial SPECT

We performed emergency ^{99m}Tc-tetrofosmin myocardial SPECT immediately before coronary angiography, during the subacute phase and the chronic phase. Patients were intravenously injected with 740 MBq of ^{99m}Tc-tetrofosmin. Early 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 gathered into an on-line 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 segments for semi-quantitation. The short-axis slices were separated into four segments at the basal and mid-ventricular levels and the apical portion of one

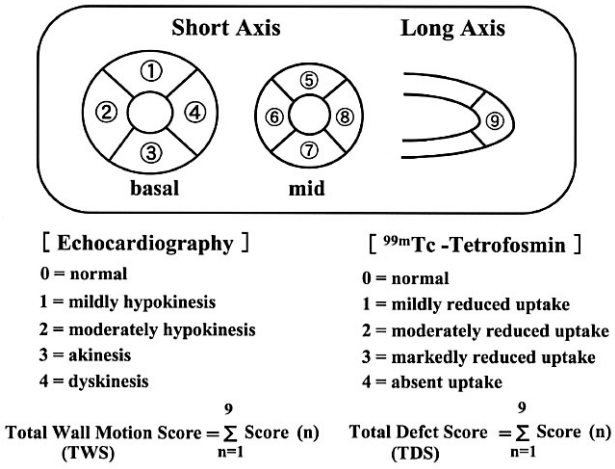

Fig. 1 Schematic representation of left ventricular segmentation. Left ventricle was divided into nine segments on two-dimensional echocardiograms and on ^{99m}Tc-tetrofosmin myocardial SPECT. Each segment on two-dimensional echocardiograms was visually graded by five points scores. The sum of each score was defined as the total wall motion score (TWS), reflecting the severity of impaired left ventricular wall motion. Each segment on ^{99m}Tc-tetrofosmin myocardial SPECT was visually graded using five points. The sum of each score was defined as the total defect score, reflecting the severity of impaired myocardial perfusion.

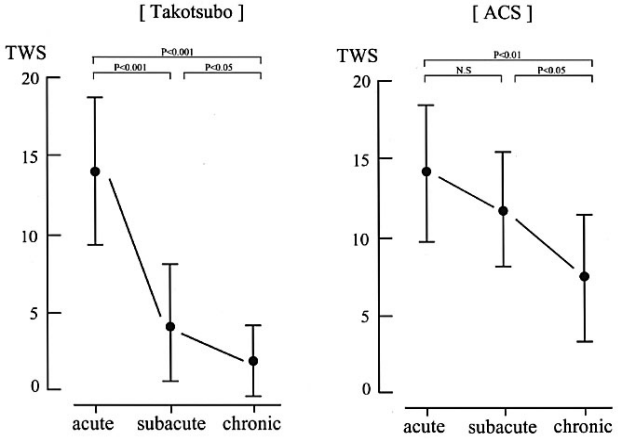

Fig. 2 Serial changes of total wall motion score (TWS) on two-dimensional echocardiograms from patients with *Takotsubo* cardiomyopathy and acute coronary syndrome. The TWS value on two-dimensional echocardiography in patients with *Takotsubo* cardiomyopathy was 13.8 ± 4.4 during the acute phase, 4.4 ± 3.8 during the subacute phase and 1.8 ± 2.3 during the chronic phase. It was 13.9 ± 4.0, 11.7 ± 3.7 and 7.6 ± 4.2, respectively in patients with acute coronary syndrome.

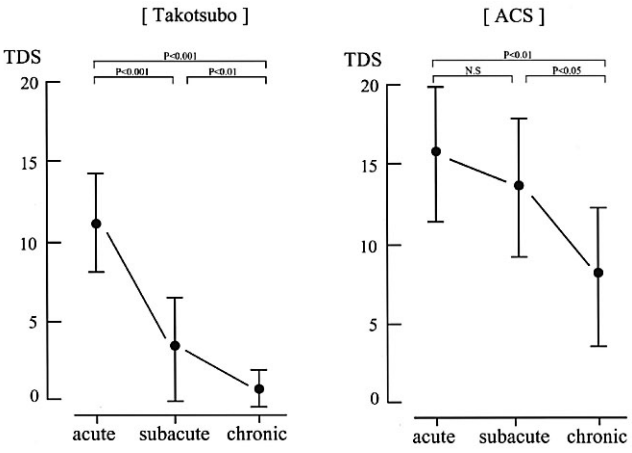

Fig. 3 Serial changes in total defect score (TDS) on ^{99m}Tc-tetrofosmin myocardial SPECT images in patients with *Takotsubo* cardiomyopathy and acute coronary syndrome. The TDS value on ^{99m}Tc-tetrofosmin myocardial SPECT images in patients with *Takotsubo* cardiomyopathy was 11.4 ± 3.2 during the acute phase, 3.2 ± 3.3 during the subacute phase and 0.7 ± 1.1 during the chronic phase. It was 15.8 ± 4.1, 13.5 ± 4.4 and 8.2 ± 4.4, respectively in patients with acute coronary syndrome.

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, markedly reduced uptake; 4, absent) 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 defect score, reflecting the severity of impaired myocardial perfusion (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. Ergonovine was injected within 30 seconds, with a 40 μg dose for the right coronary artery and a 60 μg dose for the left coronary artery. Acetylcholine was also injected within 30 seconds, with a 50 μg dose for the right coronary artery and a 100 μg dose for the left coronary artery. In patients with acute coronary syndrome, restenosis was ruled out during the chronic phase.

Left ventriculography

All patients underwent left ventriculography during the acute phase and chronic phase, and ejection fraction of the left ventricle was calculated by the Simpson method. Three patients also underwent right ventriculography during the acute phase and chronic phase.

Statistical processing

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

All participants in this study gave written informed consent to participate in all necessary procedures.

RESULTS

1) The total elevation of the ST segment on electrocardiograms (mm) was 7.9 ± 3.4 in patients with *Takotsubo* cardiomyopathy and 7.3 ± 3.7 in patients with acute coronary syndrome (N.S.).
2) The maximal value of CK-MB (normal; –25 IU/*l*) was 34 ± 23 in patients with *Takotsubo* cardiomyopathy and 326 ± 98 in patients with acute coronary syndrome ($p < 0.001$).
3) The plasma norepinephrine concentration was increased in five of 6 patients (normal; –0.31 ng/m*l*).
4) The TWS value on two-dimensional echocardiography in patients with *Takotsubo* cardiomyopathy was 13.8 ± 4.4, 4.4 ± 3.8 and 1.8 ± 2.3 during the acute phase, the subacute phase and the chronic phase, respectively. In patients with acute coronary syndrome, it was 13.9 ± 4.0, 11.7 ± 3.7, and 7.6 ± 4.2, respectively (Fig. 2).
5) The TDS value on ^{99m}Tc-tetrofosmin myocardial SPECT in patients with *Takotsubo* cardiomyopathy was 11.4 ± 3.2, 3.2 ± 3.3 and 0.7 ± 1.1 during the acute phase, the subacute phase and the chronic phase, respectively. In patients with acute coronary syndrome, it was 15.8 ± 4.1, 13.5 ± 4.4 and 8.2 ± 4.4, respectively (Fig. 3).
6) The number of segments in which ^{99m}Tc-tetrofosmin uptake was absent during the acute phase was 0.5 ± 0.8 and 3.6 ± 2.8 in patients with *Takotsubo* cardiomyopathy and acute coronary syndrome, respectively ($p < 0.01$).
7) Ejection fraction on left ventriculography was 43.8 ± 4.3% in patients with *Takotsubo* cardiomyopathy and 38.7 ± 8.6% in patients with acute coronary syndrome during the acute phase (N.S.). It was 72.3 ± 4.5 and 47.8 ± 9.2, respectively during the chronic phase ($p < 0.01$). Right ventriculography was performed in three patients, all of whom showed apical ballooning akinesis and basal hyperkinesis.

Case presentation

A 57-year-old woman presented at our hospital with a chief complaint of chest oppression. On admission, electrocardiography showed elevated ST segments in leads I, aV_L, V_{1-5}, and two-dimensional echocardiography revealed apical ballooning akinesis and basal hyperkinesis (Fig. 4-a). ^{99m}Tc-tetrofosmin myocardial SPECT showed that uptake was severely reduced, but not absent, from the mid portion to the apical area. Left ventriculography also showed apical ballooning akinesis and basal hyperkinesis (Fig. 4-b). On the fifth day, those findings had become normal (Fig. 4-c,d).

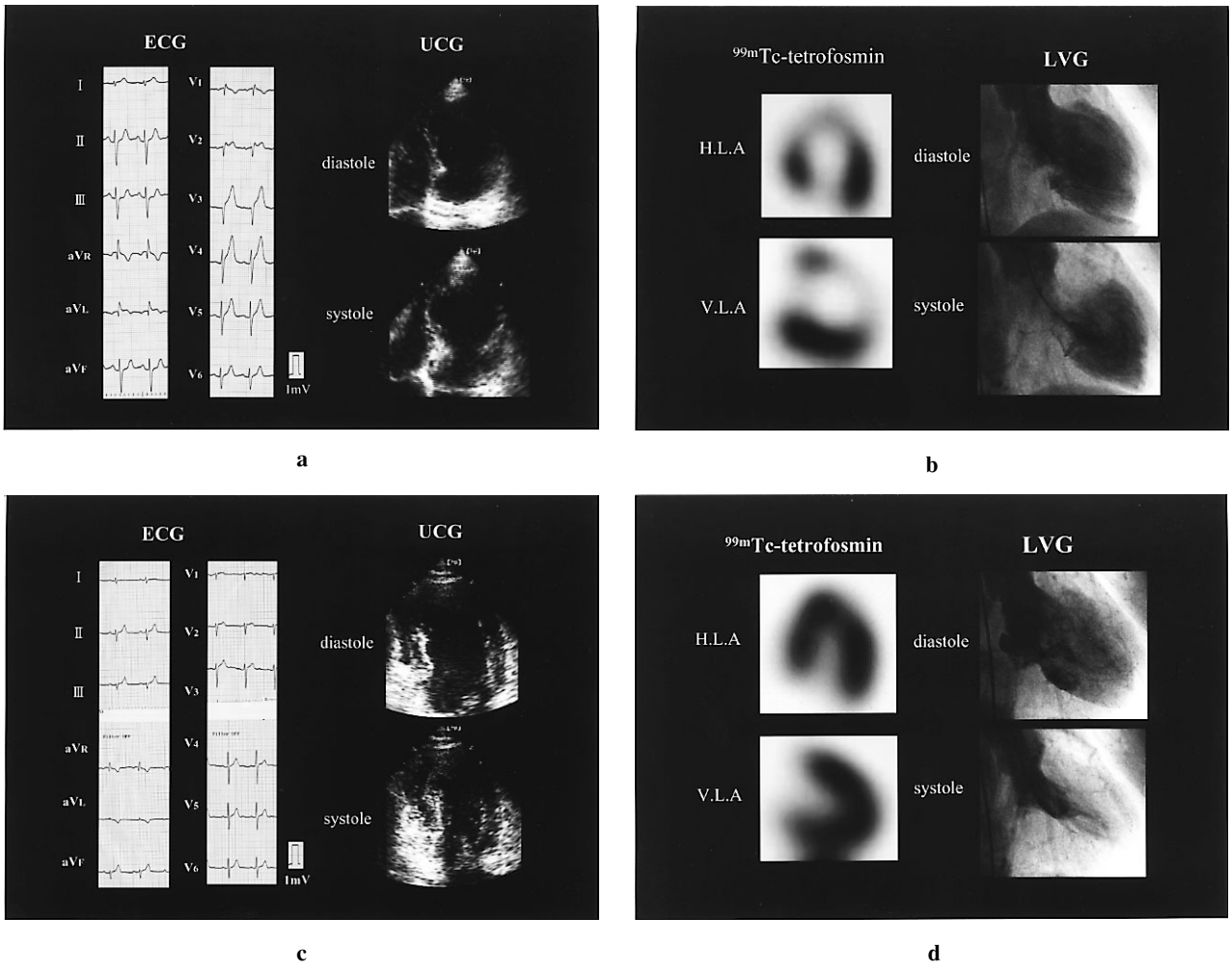

Fig. 4 Case presentation. a: An electrocardiogram showed elevated ST segments in leads I, aV_L, $V_{1–5}$ and two-dimensional echocardiography revealed apical ballooning akinesis and basal hyperkinesis during the acute phase. b: ^{99m}Tc-tetrofosmin myocardial SPECT showed that uptake was severely reduced from the mid portion to the apical area, and left ventriculography showed apical ballooning akinesis and basal hyperkinesis during the acute phase. c, d: On the fifth day, electrocardiogram, ^{99m}Tc-tetrofosmin myocardial SPECT and left ventricular wall motion on two-dimensional echocardiography and left ventriculography had become normal.

DISCUSSION

Several reports have described transient left ventricular apical ballooning akinesis and basal hyperkinesis without coronary stenosis in association with *Takotsubo* cardiomyopathy.[1–5] This syndrome accounts for about 1% of all suspected acute coronary syndrome in these reports, and 1.7% (10/573) in the present study. These reports also suggested that multiple spasms of epicardial coronary arteries, microcirculation disturbance or myocardial damage induced by catecholamines might be a causative mechanism, but this has remained a matter of speculation. The present study assessed *Takotsubo* cardiomyopathy using electrocardiography, blood tests, two-dimensional echocardiography, coronary angiography, left ventriculography and ^{99m}Tc-tetrofosmin myocardial SPECT.

^{99m}Tc-tetrofosmin can be labeled easily in the hospital, and myocardial perfusion can be visualized on SPECT images with ^{99m}Tc-tetrofosmin. In addition, ^{99m}Tc-tetrofosmin myocardial SPECT can be performed even during the acute phase in patients with acute myocardial infarction. This procedure is widely applied to diagnosing ischemic heart diseases and to evaluating pathological conditions.[6,7]

Sudden onset with chest symptoms, elevated ST segments on electrocardiograms and severely reduced left ventricular wall motion were demonstrated in patients with *Takotsubo* cardiomyopathy in this study as they have been in previous reports. The degree of elevated ST segment and abnormal wall motion did not significantly differ between the two groups. Furthermore, ^{99m}Tc-tetrofosmin images showed that myocardial uptake was

severely reduced in all patients of both groups during the acute phase. These findings suggested that myocardial ischemia is closely related to the causative mechanism of *Takotsubo* cardiomyopathy.

None of the epicardial coronary arteries of the patients with *Takotsubo* cardiomyopathy showed evidence of spasm. Thus, multiple spasms of epicardial coronary arteries were not considered to be relevant, whereas impaired coronary microcirculation[15,16] seemed to be a causative mechanism of *Takotsubo* cardiomyopathy. The epicardial coronary artery ramifies into a network of small vessels, such as the subepicardial artery (200 μm), intramuscular arteriole (100–30 μm), precapillaries (20–10 μm), capillaries (8–5 μm), and venules.[17] 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.[17,18] In *Takotsubo* cardiomyopathy, coronary angiography revealed patency during the acute phase with ST elevation on electrocardiograms and akinesis on left ventriculography. 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.[19,20] 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, patent epicardial coronary flow was observed during the acute phase with ST segment elevation on the electrocardiogram.[21,22]

Coronary microvascular spasm[21–23] or coronary microvascular diastolic functional abnormalities[15,16] 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 acute myocardial infarction. Microvascular spasm might be a mechanism underlying myocardial ischemia in patients with *Takotsubo* cardiomyopathy.

Many patients developed *Takotsubo* cardiomyopathy after enduring psychological stress such as an accident involving a family member, the death of a loved one, a quarrel and vigorous excitation. Under such stressful situations, excess norepinephrine might be secreted from the sympathetic nervous system, which might provoke microvascular spasm via α2 receptors.[24] Sympathetic nerves are also distributed to smaller vessels such as intramuscular arterioles, but parasympathetic nerves are only distributed to the epicardial and subepicardial arteries.[25] Therefore the influence of the sympathetic nerve extends to the coronary microcirculation. When pigs are subjected to restraint stress, electrocardiograms show negative T wave and/or elevation of the ST segment in 61% of them, with 13% suddenly dying.[26] Myocardial ischemia is induced in humans by psychological stress, and the risk of sudden cardiac death increases with high levels of such stress.[27–30] Emotional stress induces transient reductions of left ventricular wall motion like the *Takotsubo* like shape in rat and this can be normalized by prior adrenoceptor blockade.[31] Six of 10 patients in this study were psychologically stressed at the time of the attack, which may have caused excessive secretion of catecholamines and abnormally increased coronary microvascular tonus, namely spasm. However, no definitive psychological stress was evident in the other 4 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 six patients in the present study. In the present study, three patients also revealed apical akinesis and basal hyperkinesis of the right ventricle. This phenomenon suggested that an imbalance in neurohumoral factors and/or excessive catecholamine secretion 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 region of the left ventricle, the number of sympathetic nervous endings is decreased whereas the number of receptors is increased. The opposite is true in the basal region of the left ventricle.[32] 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 to be clarified.

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 during the acute phase and of improved wall motion during the subacute and chronic phases were significantly higher in patients with *Takotsubo* cardiomyopathy. Myocardial damage in patients with *Takotsubo* cardiomyopathy was transient like 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 did not uptake any myocardial ^{99m}Tc-tetrofosmin. These results suggested that slight residual myocardial perfusion persisted during the acute phase in patients with *Takotsubo* cardiomyopathy. Such residual myocardial perfusion could preserve fundamental myocardium functions such as that

of the membrane, while myocardial damage is reduced but could be improved during the early phase as it is in the stunned myocardium.

The present study showed that impaired microcirculation might be a causative mechanism of Takotsubo cardiomyopathy, 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, Oh-mura 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. Veretto T, Cantalupi D, Altieri A, Orlamdi C. Emergency room technetium-99m-sestamibi imaging to rule out acute myocardial ischemic events in patients with nondiagnostic electrocardiogram. *J Am Coll Cardiol* 1993; 22: 1804–1808.
8. Braunwald E, Kloner RA. The stunned myocardium: prolonged, postischemic ventricular dysfunction. *Circulation* 1982; 66: 1146–1149.
9. Kono T, Morita H, Kuroiwa T, Onaka H, Takatsuka H, Fujiwara A. Left ventricular wall motion abnormalities in patients with subarachnoid hemorrhage: neurogenic stunned myocardium. *J Am Coll Cardiol* 1994; 24: 636–640.
10. Sakamoto H, Nishimura H, Imataka K, Ieki K, Horie T, Fuji J. Abnormal Q wave, St-segment elevation, T wave inversion and widespread focal myocytolysis associated with subarachnoid hemorrhage. *Jpn Circ J* 1996; 60: 254–257.
11. Ohtsuka T, Hamada M, Kodama K, Sasaki O, Suzuki M, Hara Y, et al. Neurogenic stunned myocardium. *Circulation* 2000; 101: 2122–2124.
12. Shaw TRD, Bafferty P, Tait GW. Transient shock and myocardial impairment caused by pheochromocytoma. *Br Heart J* 1987; 57: 194–198.
13. 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.
14. 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.
15. Kemp HG. Left ventricular function in patients with the anginal syndrome and normal coronary arteriograms. *Am J Cardiol* 1973; 32: 375–376.
16. Cannon RO, Epstein SE. Microvascular angina as a cause of chest pain with angiographically normal coronary arteries. *Am J Cardiol* 1988; 61: 1338–1343.
17. Sherf L, Ben-Shaul Y, Lieberman Y, Neufeld HN. The human coronary circulation: An electron microscopic study. *Am J Cardiol* 1977; 39: 599–607.
18. Guzman SV, Swenson E, Jones M. Intracoronary reflex. Demonstration by coronary angiography. *Circ Res* 1962; 10: 739–745.
19. Hori M, Inoue M, Kitakaze M, Koresune Y, Iwai K, Tamai J, et al. Role of adenosine in hyperemic response of coronary blood flow in microembolization. *Am J Physiol* 1986; 250: H509–518.
20. 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: H244–251.
21. 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.
22. Serota H, Kern MJ, Deligonul U, Aguirre F, Caralis DG. Ergonovine-induced myocardial ischemia without epicardial coronary vasospasm: evidence for ischemia produced by small-vessel vasoconstriction. *Am Heart J* 1991; 121: 1807–1809.
23. Mohri M, Koyanagi M, Egashira K, et al. Angina pectoris caused by coronary microvascular spasm. *Lancet* 1998; 351: 1165–1169.
24. Berne RM. Coronary circulation. In *Handbook of Physiology*. Vol. I The heart ed. by Berne RM et al. Bethesda; American Physiological Society, 1979: 873.
25. Hirsch EF, Broghard-Erdle AM. The innervation of the human heart. I. The coronary arteries and the myocardium. *Arch Pathol* 1961; 71: 384–407.
26. Johansson G, Jonesson L, Lannek N, Blomgren L, Lindberg P, Poupa O. Severe stress-cardiopathy in pigs. *Am Heart J* 1987; 87: 451–457.
27. Leor J, Poole WK, Kloner RA. Sudden cardiac death triggered by an earthquake. *N Engl J Med* 1996; 334: 413–419.
28. Frustaci Q, Loperfido F, Gentiloni N, Caldarulo M, Morgante E, Russo MA. Catecholamine-induced cardiomyopathy in multiple endocrine neoplasia: A histologic, ultrastructural, and biochemical study. *Chest* 1991; 99: 382–385.
29. Yamabe H, Hanaoka J, Funakoshi T, Iwahashi M, Takeuchi M, Saito K, et al. Deep negative T waves and abnormal cardiac sympathetic image (^{123}I-MIBG) after the great Hanshin earthquake of 1995. *Am J Med Sci* 1996; 311: 221–224.
30. Cebelin MS, Hirsch CS. Human stress cardiomyopathy: Myocardial lesions in victims of homicidal assaults without internal injuries. *Hum Path* 1980; 11: 123–132.
31. 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. *Jpn Circ J* 2002; 66: 712–713.

32. Murphree SS, Saffitz JE. Quantitative autoradiograpic delineation of the distribution of beta-adrenergic receptors in canine and feline left ventricular myocardium. *Circ Res* 1987; 60: 568–579.