

Assessment of ampulla (*Takotsubo*) cardiomyopathy with coronary angiography, two-dimensional echocardiography and ^{99m}Tc -tetrofosmin myocardial single photon emission computed tomography

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We studied the causative mechanism of ampulla (*Takotsubo*) cardiomyopathy. **Methods:** We examined 7 patients with ampulla cardiomyopathy by means of coronary angiography, two-dimensional echocardiography and ^{99m}Tc -tetrofosmin myocardial SPECT at the time of emergency admission (acute phase), at 3 to 5 days after the attack (subacute phase) and at 1 month after the attack (chronic phase). The left ventricle was divided into 9 regions on two-dimensional echocardiograms and ^{99m}Tc -tetrofosmin myocardial SPECT images, then the degree of abnormalities in each region was scored in four grades from normal (0) to severely abnormal (3). We injected nicorandil into the coronary arteries and determined the elevation in the ST segment before and after administration. **Results:** Coronary angiography did not show stenotic lesions in any patient. The acute, subacute and chronic phase myocardial perfusion scores on ^{99m}Tc -tetrofosmin myocardial SPECT were 11.2 ± 3.4 , 2.7 ± 2.3 and 0.4 ± 0.5 , respectively, and wall motion scores on echocardiograms were 13.0 ± 3.6 , 4.4 ± 2.2 and 0.6 ± 0.6 , respectively, indicating improvement in all scores during the subacute phase ($p < 0.01$). The elevation in the ST segment (mm) on the electrocardiogram was improved from 8.3 ± 2.7 to 4.9 ± 1.9 after the administration of nicorandil ($p < 0.05$). **Conclusion:** These findings indicated that coronary microvascular spasm is one causative mechanism of ampulla cardiomyopathy.

Key words: ampulla (*Takotsubo*) cardiomyopathy, microvascular spasm, nicorandil, ^{99m}Tc -tetrofosmin

INTRODUCTION

LEFT VENTRICULOGRAPHY of patients with ampulla (*Takotsubo*) cardiomyopathy showed a balloon-like asynergy of the apical regions, elevation in the ST segment on the electrocardiograms, and minimal increase in cardiac enzymes in blood tests. These patients are usually misdiagnosed as having acute myocardial infarction and undergo coronary angiography and left ventriculography,

but coronary angiography does not show stenotic lesions, even during the acute phase with elevation in the ST segment on the electrocardiograms. Furthermore, ventricular dysfunction usually improves within several weeks. The causative mechanism of ampulla cardiomyopathy remains unknown.^{1,2}

We studied the causative mechanism of ampulla cardiomyopathy by means of coronary angiography, two-dimensional echocardiography and ^{99m}Tc -tetrofosmin myocardial single photon emission computed tomography (SPECT).^{3–5}

PATIENTS

We studied seven patients with ampulla cardiomyopathy

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(Table 1) who satisfied the following criteria (5 females and 2 males; mean age 65.1 ± 6.8 years).

1) Symptoms that resembled those of acute myocardial infarction.

2) Absence of organic stenotic lesions in the epicardial coronary arteries and spasms of epicardial coronary arteries ruled out by ergonovine or acetylcholine loading tests.

3) Severely abnormal ventricular wall motion of the left ventricular apex during the acute phase that rapidly improved.

4) Absence of underlying diseases such as subarachnoid hemorrhage or other cerebrovascular disorders, head trauma or pheochromocytoma.

METHODS

Blood tests

The MB fraction of creatine phosphokinase (CK-MB) was measured every 6 hours starting immediately after admission until 72 hours after the attack (Fig. 1).

Coronary angiography

All patients underwent coronary arteriography during the acute phase. Three to 5 mg of isosorbide dinitrate was injected directly into the coronary arteries during the procedure, and 1.2 mg of nicorandil dissolved in 10 ml of physiological saline was injected directly into the coronary arteries. Coronary arteriography was again performed at 5 to 14 days after the attack, along with coronary spasm provocation tests with ergonovine or acetylcholine loading. Ergonovine was loaded by injecting directly into the left and right coronary arteries in escalating doses of 10, 20 and 30 μg up to a total dose of 60 μg . Acetylcholine was loaded in a similar manner in escalating doses of 10, 20, 50 and 100 μg up to a total dose of 180 μg (Fig. 2).

$^{99\text{m}}\text{Tc}$ -tetrofosmin myocardial SPECT

We performed emergent $^{99\text{m}}\text{Tc}$ -tetrofosmin myocardial SPECT immediately before coronary arteriography during the acute phase. $^{99\text{m}}\text{Tc}$ -tetrofosmin myocardial SPECT was reexamined during the subacute phase at 3 to 5 days after the attack and during the chronic phase at 1 month after the attack (Fig. 1). Patients were intravenously injected with 740 MBq of $^{99\text{m}}\text{Tc}$ -tetrofosmin (Nihon Medi-Physics Co., Nishinomiya, Japan), then early SPECT images were obtained starting 10 minutes later. Images were acquired with a digital gamma camera 901A (Toshiba Co., Tokyo, Japan) to which a low energy, high-resolution, parallel-hole collimator was attached. Data were collected 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. Data were acquired in an on-line nuclear medicine data processor, GMS550U (Toshiba Co., Tokyo, Japan). The original image was reconstituted by smoothing at 5 points. Tomographic images along the

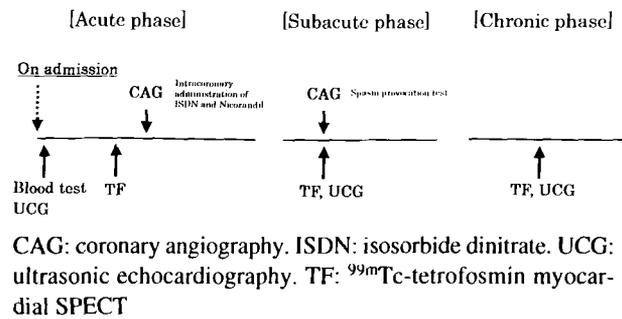
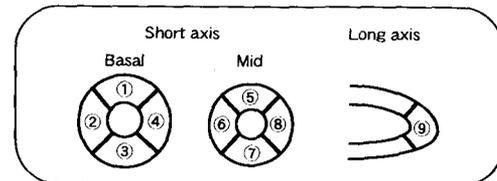


Fig. 1 Study protocol.



[Tetrofosmin]

Defect Score (DS)

- 0 = normal uptake
- 1 = mildly reduced
- 2 = moderately reduced
- 3 = severely reduced

$$\text{total defect score (TDS)} = \sum_{n=1}^9 \text{DS} (n)$$

[Echocardiography]

Wall Motion Score (WS)

- 0 = normal
- 1 = mild hypokinesia
- 2 = moderate hypokinesia
- 3 = akinesia

$$\text{total wall motion score (TWS)} = \sum_{n=1}^9 \text{WS} (n)$$

Fig. 2 Schematic representation of left ventricular segmentation. The left ventricle was divided into 9 segments on SPECT images and on two-dimensional echocardiographs: 1 and 5, anterior; 2 and 6, septal; 3 and 7, inferior; 4 and 8, lateral; 9, apical.

vertical long, horizontal long and short axis were created with a Shepp & Logan filter. The threshold level was 20% and absorption was not corrected. The SPECT image of the left ventricle was divided into 9 segments for semi-quantitative analysis. The short-axis slices were separated into four segments at the basal and midventricular levels. The apical portion of one segment was evaluated with vertical long-axis slices. Each segment was graded visually with scores between 0 and 3 (0, normal; 1, mildly reduced uptake; 2, moderately reduced uptake; 3, obviously reduced uptake/absent activity) 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. 2).

Two-dimensional echocardiograms

All patients underwent two-dimensional echocardiography during the acute phase, subacute phase and chronic phases and were examined with a Sonos 5500 (Hewlett-Packard, Cal, USA). The tomographic image of the left ventricle obtained from the short axial image of the sternal left edge and the long axial image of the apex of the heart was divided into 9 segments. Each segment was graded visually with scores between 0 and 3 (0, normal; 1, mild

Table 1 Clinical characteristics

Case No.	Gender/age	Underlying disorder	Trigger event	Symptoms	ECG ST elevation	Left ventricular ejection fraction (%) acute/chronic phase	Level of CPK-MB (-25 IU/l)
1	F/72	Hypertension	Emotional stress (+): an accidental death of her sister	Chest pain	II, III aVF, V ₂₋₆	45%→78%	16
2	F/73	None	None	Dyspnea, chest oppression	I, aV ₁ , V ₂₋₆	50%→68%	24
3	M/56	Chronic pancreatitis	Emotional stress (+): Endoscopic retrograde cholangiopancreatography (ERCP)	Chest pain, back pain	I, II, III, aV ₁ , V ₂₋₅	38%→74%	73
4	F/62	Hypertension Hyperlipidemia	Emotional stress (+): dispute	Dyspnea	I, aV ₁ , V ₁₋₅	47%→71%	20
5	F/58	Hypertension	None	Syncope, Chest oppression	II, III, aVF, V ₂₋₆	45%→69%	15
6	M/65	Hepatic cirrhosis esophageal varix	Emotional stress (+): Balloon occluded-retrograde Transvenous obliteration (B-RTO)	Chest pain	I, II, III, aV ₁ , V ₂₋₆	42%→80%	59
7	F/70	None	None	Chest discomfort, Dyspnea	II, III, aVF, V ₂₋₅	49%→67%	23

hypokinesia; 2, moderate hypokinesia; 3, akinesia) 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. 2).

Statistical processing

Values are expressed as means \pm standard deviation. The ANOVA F test was used to examine 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 all necessary procedures.

RESULTS

1) The maximal value of CK-MB during the study was 32.9 ± 23.1 (IU/l), and values exceeded twice the normal upper limit (25 IU/l) in 2 patients (Table 1).

2) The TDS values on ^{99m}Tc -tetrofosmin myocardial SPECT during the acute, subacute and chronic phases were 11.2 ± 3.4 , 2.7 ± 2.3 , 0.4 ± 0.5 , respectively, indicating improvement during the subacute phase ($p < 0.01$; Fig. 3).

3) The TWS values on two-dimensional echocardiography during the acute, subacute and chronic phases were 13.0 ± 3.6 , 4.4 ± 2.2 and 0.6 ± 0.6 , respectively, also indicating improvement during the subacute phase ($p < 0.01$;

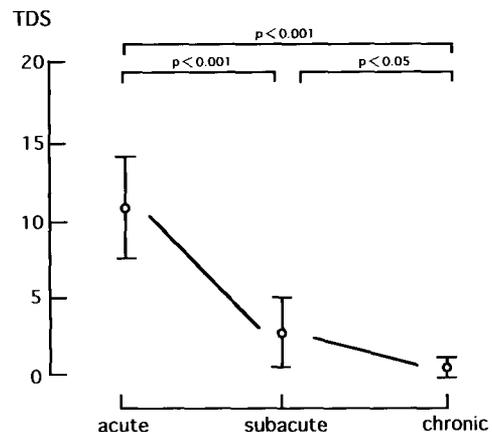


Fig. 3 Serial changes in total defect score (TDS) on ^{99m}Tc -tetrofosmin myocardial SPECT images. The TDS values on early tetrofosmin images in the acute, subacute and chronic phases were 11.2 ± 3.4 , 2.7 ± 2.3 , 0.4 ± 0.5 , respectively, indicating improvement during the subacute phase ($p < 0.01$).

Fig. 4).

4) Three to 5 mg of isosorbide dinitrate injected into the coronary artery did not reduce the elevation in the ST segment in any of those patients.

5) Nicorandil (1.2 mg) injected into the coronary arteries reduced the elevation in the ST segments in 5 of 7 patients on electrocardiograms from 8.6 ± 2.9 to 5.4 ± 2.4 ($p < 0.05$; Fig. 5).

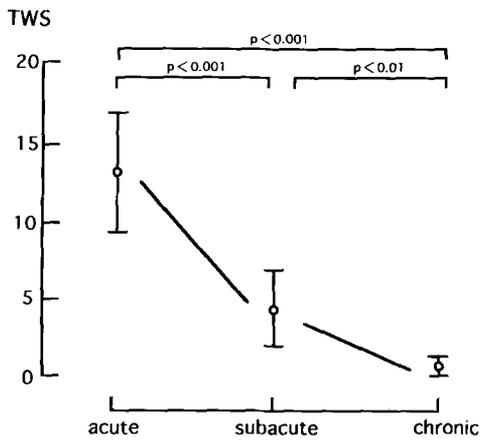


Fig. 4 Serial change of total wall motion score (TWS) on two-dimensional echocardiography. The TWS values on two-dimensional echocardiography during the acute, subacute and chronic phases were 12.2 ± 3.1 , 4.2 ± 2.1 and 0.5 ± 0.5 , respectively, indicating improvement during subacute phase ($p < 0.01$).

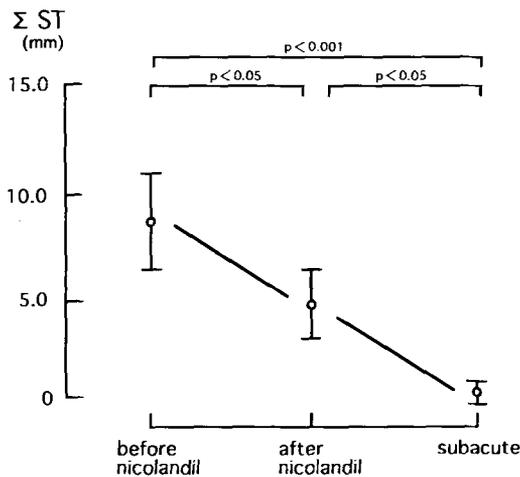
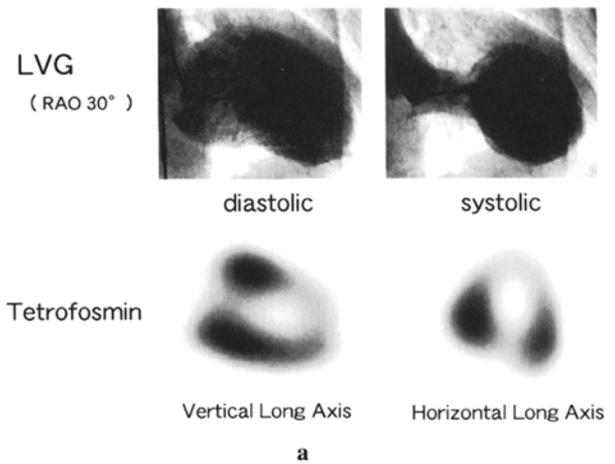


Fig. 5 Serial changes of total degree of elevation in the ST segment on electrocardiogram. Nicorandil administered into the coronary arteries improved elevation in the ST segments in 5 of 7 patients on electrocardiograms from 8.6 ± 2.9 to 5.4 ± 2.4 ($p < 0.05$).

CASE REPORT

A 48-year-old man presented at our hospital with a chief complaint of chest pain. On admission, an electrocardiogram showed an elevation in the ST segment in leads I, aVL and V_{1-4} . ^{99m}Tc -tetrofosmin myocardial SPECT revealed severely reduced uptake from the mid portion to the apical area (Fig. 6a). Although no stenotic lesion was revealed by coronary arteriography, left ventricular wall motion was severely hypokinetic from the mid portion to the apical area on left ventriculography (Fig. 6a). After the intracoronary administration of nicorandil, elevation in the ST segment on the electrocardiogram was improved.

Acute phase



Subacute phase

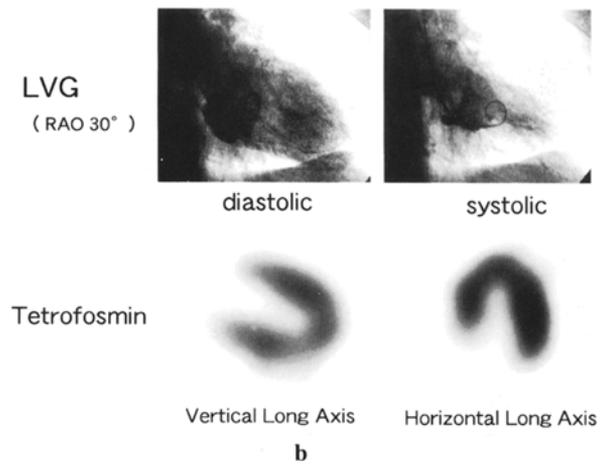


Fig. 6 Case report. (a) In acute phase, ^{99m}Tc -tetrofosmin myocardial SPECT showed severely reduced uptake from the mid portion to the apical area, and left ventriculography display a balloon-like asynergy of the apical regions. (b) In subacute phase, ^{99m}Tc -tetrofosmin myocardial SPECT did not show reduced uptake, and left ventriculography revealed normal findings.

On the third day, ^{99m}Tc -tetrofosmin myocardial SPECT did not show reduced uptake (Fig. 6b). On the seventh day, left ventriculography showed normal findings (Fig. 6b).

DISCUSSION

Decreased uptake on ^{99m}Tc -tetrofosmin myocardial SPECT images, elevation in the ST segment on electrocardiograms and severe left ventricular dysfunction on echocardiograms during the acute phase suggested severe myocardial ischemia, but coronary arteriography did not show any stenotic lesions of the epicardial coronary arteries. These results suggest that impaired coronary

microcirculation is a causative mechanism of myocardial ischemia. Coronary microvascular spasm⁶⁻⁸ or coronary microvascular diastolic functional abnormalities^{9,10} are considered to be causes of impaired coronary microcirculation, but when myocardial ischemia is caused by impaired coronary microvascular diastolic functional abnormalities, electrocardiography does not show any elevation in the ST segment, and two-dimensional echocardiography does not reveal severe dysfunction. Microvascular spasm is considered to be a plausible mechanism of myocardial ischemia. The thoracic symptoms and the elevated ST segment on electrocardiograms were improved in 5 of 7 patients after the coronary arterial administration of nicorandil. This drug acts as both a NO donor and a K_{ATP} channel opener, and it has a characteristically dilating effect on coronary microvessels,^{11,12} but myocardial ischemia in patients with ampulla cardiomyopathy might be caused by microvascular spasm.

When pigs were stressed by restraint, electrocardiograms showed a negative T wave and/or elevation in the ST segment in 61% of the animals, and 13% of the animals died suddenly. The pathological findings in the myocardium were similar to those of coronary artery ligation.¹³ Myocardial ischemia in humans can be induced by psychological stress, and the risk of sudden cardiac death increases when levels of such stress are high.¹⁴ Four of 7 patients in this study were psychologically stressed at the time of attack, which may have caused excessive secretion of catecholamines and abnormally increased coronary microvascular tonus, namely spasm, but no clear psychological stress was evident in any of the other 3 patients. An imbalance in neurohumoral factors or excessive catecholamine secretion could have caused coronary microvascular spasm, but we did not measure these parameters, so a definite conclusion cannot be reached.

This study only clarified one of the causative mechanisms of ampulla cardiomyopathy. Further studies of more patients and basic experiments are required to understand the causative mechanisms of ampulla cardiomyopathy in detail.

REFERENCES

1. Kawai S, Suzuki H, Yamaguchi H, et al. Ampulla cardi-

- omyopathy (*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. Tamaki N, Takahashi N, Kawamoto M, et al. Myocardial tomography using technetium-99m-tetrofosmin to evaluate coronary artery disease. *J Nucl Med* 1994; 35: 594–600.
4. 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.
5. Gibbons RJ. Perfusion imaging with ^{99m}Tc-sestamibi for the assessment of myocardial area at risk and the efficacy of acute treatment in myocardial infarction. *Circulation* 1991; 84: 37–42.
6. 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.
7. 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.
8. Mohri M, Koyanagi M, Egashira K, et al. Angina pectoris caused by coronary microvascular spasm. *Lancet* 1998; 351: 1165–1169.
9. Kemp HG. Left ventricular function in patients with the anginal syndrome and normal coronary arteriograms. *Am J Cardiol* 1973; 32: 375–376.
10. Cannon RO, Epstein SE. Microvascular angina as a cause chest pain with angiographically normal coronary arteries. *Am J Cardiol* 1988; 61: 1338–1343.
11. Chen JW, Lee WL, Hsu NW, et al. Effects of short-term treatment of nicorandil on exercise-induced myocardial ischemia and abnormal cardiac autonomic activity in microvascular angina. *Am J Cardiol* 1997; 80: 32–38.
12. Taira N. Nicorandil as a hybrid between nitrates and Potassium channel activators. *Am J Cardiol* 1989; 63: 18–24.
13. Johansson G, Jonesson L, Lannek N, Blomgren L, Lindberg P, Poupa O. Severe stress-cardiopathy in pigs. *Am Heart J* 1987; 87: 451–457.
14. Leor J, Poole WK, Kloner RA. Sudden cardiac death triggered by an earthquake. *N Engl Med* 1996; 334: 413–419.