A pathophysiologic study of tako-tsubo cardiomyopathy with F-18 fluorodeoxyglucose positron emission tomography

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Aims Our study aims to investigate the pathophysiologic mechanism underlying tako-tsubo cardiomyopathy using F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET).

Methods and results Fifteen patients with tako-tsubo cardiomyopathy were enrolled in this study. Plasma catecholamines, cardiac troponin T (cTnT), and D-dimer were serially evaluated in all patients. Thallium-201 (201Tl) single-photon emission computed tomography (SPECT) and F-18 FDG PET were performed in 10 and eight patients, respectively. Emotional or physical stress occurred in 12 (80.0%) patients. ST-T segment abnormalities existed in all patients. Thirteen patients exhibited mildly elevated cTnT, although coronary angiography did not reveal significant stenosis in any patient. Endomyocardial biopsy specimens (n = 9) demonstrated contraction-band necrosis (n = 4) and mononuclear cell infiltration (n = 3). The levels of norepinephrine and epinephrine peaked on admission (744 ± 452 and 140 ± 166 pg/mL, respectively). There was severely reduced uptake at the apex on F-18 FDG PET image, despite slightly reduced uptake of 201Tl. Elevation of D-dimer was observed in nine patients.

Conclusion The extent of metabolic defect involving apical akinetic area was more severe than perfusion abnormality. Our data suggest that sudden emotional or physical stress may cause a catecholamine-induced metabolic disorder in the myocardium, which is probably central to this syndrome.

KEYWORDS
Tako-tsubo cardiomyopathy; Catecholamine-induced metabolic disorder; F-18 fluorodeoxyglucose positron emission tomography

Introduction
In the past decade, transient cardiac contractile abnormalities with chest symptoms, ST-T segment changes on electrocardiography (ECG) and relatively minor myocardial enzyme release similar to acute myocardial infarction, have been reported after the sudden onset of emotional or physical stress. Some studies from Japan regarding this cardiac syndrome have indicated reversible left ventricular apical ballooning and normal coronary angiographic findings that occur with a surge in emotional or physical stress. The shape of apical ballooning associated with basal hyperkinesis and apical akinesis is sometimes described as ‘tako-tsubo cardiomyopathy’, mimicking a fishing pot with a narrow neck and wide base that is used to trap octopus in Japan. Conceivably, emotional or physical stress plays a crucial role in causing left ventricular dysfunction. Wittstein et al. reported that sudden elevations in plasma epinephrine levels after emotional or physiological stress are possibly involved in the pathogenesis of tako-tsubo cardiomyopathy. However, the pathophysiological mechanism underlying the deteriorating effect of catecholamines on the myocardium and its metabolism is not precisely understood. Against this background, we have conducted this observational study aimed at identifying the definitive pathophysiologic mechanism leading to tako-tsubo cardiomyopathy using F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) to demonstrate a metabolic myocardial image.

Methods
Patients
We evaluated 15 consecutive patients (12 females and three males with a mean age of 72 ± 7 years) from December 2002 to February 2007 who met the following criteria: (i) reversible balloon-like left ventricular wall motion abnormality at the apex with hypercontraction of the basal segment, (ii) ST-segment elevation or T-wave inversion in several leads on the ECG during the acute phase, with these abnormalities reverting to normal, (iii) no history of prior myocardial infarction or idiopathic cardiomyopathy, and (iv) no complications, such as sub-arachnoid haemorrhage or
pheochromocytoma crisis. All patients gave written informed consent to participate in the study for research and publication purposes and in all procedures associated with the study. The study complied with the Declaration of Helsinki and was approved by our institutional Ethics Committee.

The clinical characteristics recorded from the medical record included age, gender, coronary risk factors, symptoms, and a possible triggering factor. An ECG was performed every hospital day during the acute phase. Echocardiography was performed to clarify balloon-like left ventricular wall motion abnormalities during the acute phase and its recovery. Cardiac isoenzymes, including creatine kinase (CK), creatine kinase MB (CK-MB) sub-fraction, and cardiac troponin T (cTnT), were serially measured in all patients. Plasma levels of norepinephrine, epinephrine, brain natriuretic peptide (BNP), and D-dimer were also serially measured during the hospital stay. Blood samples were obtained every 12 h during the first 24 h after admission and once daily beginning on the second day to determine the peak level. Samples were placed on ice and immediately centrifuged, and the plasma was flash-frozen. Plasma levels of catecholamines were measured by high-performance liquid chromatography. D-dimer was measured by latex agglutination; BNP was measured by an immunodiagnostic assay using two monoclonal antibodies. Viral antibody titres were evaluated on admission and 4 weeks thereafter in all patients, a four-fold rise in viral antibody titres was considered significant.

Cardiac catheterization

Coronary angiography and measurements of cardiac output and pulmonary capillary wedge pressure via a Swan–Ganz catheter were performed in 14 patients by the femoral approach after intravenous infusion of 3000 U of heparin within 24 h after onset of symptoms. According to the clinical indication, we performed coronary angiography during both the acute and the chronic phase in four patients who presented in cardiogenic shock, measuring the intraventricular pressure gradient or lower left ventricular ejection fraction. Coronary artery disease was defined as >50% stenosis in the luminal diameter of the major epicardial coronary artery. Left ventriculography was performed in the 30° right anterior oblique projection to calculate the left ventricular ejection fraction by means of the area-length method. We also performed the coronary spasm provocation test by intracoronary infusion of acetylcholine in six patients during the acute phase (50 μg to the right coronary artery and 100 μg to the left coronary artery). We defined coronary spasm as a reduction in diameter of >75% compared with the diameter before intracoronary infusion of acetylcholine. After acute angiograms were obtained to determine the underlying cardiac disease, endomyocardial biopsies were performed in nine patients under fluoroscopic control to gain three to five samples from the area around the left ventricular apex where asynergy was observed. Samples were immediately fixed in 4% buffered formalin and embedded in paraffin. For each sample, 4 μm paraffin sections were stained with haematoxylin and eosin. Light microscopy was performed and tissue samples were reviewed by three experienced pathologists.

201Tl myocardial single-photon emission computed tomography

Ten patients underwent rest thallium-201 (201Tl) single-photon emission computed tomography (SPECT) on an E.CAM Signature System™ (Toshiba Co. Ltd, Tokyo, Japan) during the acute phase. After overnight fasting, an intravenous bolus injection of 201Tl (111 MBq) was performed at rest, and data acquisition was started 20 min after radionuclide injection using a two-headed SPECT system with low-energy, all-purpose, parallel-hole collimators. A total of 60 projection images were obtained in a 64 x 64 matrix over 360°, with 30 s per view. After reduction of the matrix size of the projection data, tomographic images along the vertical-long, horizontal-long, and short-axis were created. SPECT images of the left ventricle were divided into 17 segments for semi-quantitative analysis.

F-18 fluorodeoxyglucose myocardial positron emission tomography

The PET scans with F-18 FDG were performed on a GE Advance PET camera™ (GE Medical System, Waukesha, WI, USA) in eight patients 8 ± 3 days after the onset of symptoms. All studies were conducted after a 12 h fast. Three-minute emission and seven-minute transmission scans were obtained for optimal positioning and for subsequent attenuation correction. A PET study was performed 40 min following the injection of 5 MBq/kg of F-18 FDG after a 75 g glucose load. Emission images were then corrected for attenuation, scatter, random coincidences, dead time, and radioactive decay. The reconstructed images were displayed in short-axis and horizontal and vertical long-axis views. Both the SPECT and PET images were interpreted by consensus of two experienced observers using a 16-slice model of the left ventricle.

Statistical analyses

Statistical analyses were performed on a personal computer with JMP software, version 5.1 (SAS Institute, Cary, NC, USA). Continuous variables are expressed as the mean ± SD, unless otherwise indicated. The Wilcoxon signed-rank test was used to compare the left ventricular ejection fractions between the acute and chronic phases. A two-tailed P-value of < 0.05 was considered to indicate statistical significance.

Results

Characteristics of patients and possible triggering factors

The characteristics of the patients are presented in Table 1. The mean age of the patients was 72 ± 7 years (range 64–83 years), 12 patients (80.0%) were female, and the duration of hospital stay was 10–62 days. None of the patients had a

| Age (years) | 72 ± 7 |
| Female/male | 12/3 |
| Coronary risk factors | |
| Hypertension | 3 (20.0%) |
| Diabetes mellitus | 2 (13.3%) |
| Hyperlipidaemia | 1 (6.7%) |
| Current smoking | 4 (26.7%) |
| Symptoms | |
| Chest pain or discomfort | 13 (86.7%) |
| Cardiogenic shock | 1 (6.7%) |
| Triggering factors | |
| Physical stress | |
| Medical treatment | 5 (33.3%) |
| Alcohol | 1 (6.7%) |
| Emotional stress | |
| Death of spouse | 2 (13.3%) |
| Death of grandchild | 1 (6.7%) |
| Human relations | 2 (13.3%) |
| Public performance | 1 (6.7%) |
| Unknown | 3 (20.0%) |

Values are number of patients (%) or mean ± SD (n = 15).
history of previous heart disease. Thirteen patients (86.7%) had chest pain or discomfort similar to an acute myocardial infarction at the time of presentation for evaluation. One patient who was presented in cardiogenic shock required intra-aortic balloon counterpulsation on admission for haemodynamic support, and then needed medication comprising diuretics, dopamine, and dobutamine for heart failure complicated with tako-tsubo cardiomyopathy during the hospital stay. Angiotensin II receptor antagonists were used for the treatment of hypertension in three patients (20.0%), and calcium antagonists were given to three patients who exhibited coronary spasm in the provocation test. None of the patients received treatment with angiotensin-converting enzyme inhibitors or β-blockers. Possible triggering factors were physical stress in six patients (40.0%) and emotional stress in six patients (40.0%) before the onset of symptoms. The remaining three patients (20.0%) experienced no such specific conditions.

**Electrocardiography findings**

All patients were in sinus rhythm on the initial ECG. In 13 patients (86.7%), ST-segment elevations of at least 1 mm were observed in several leads, especially in V3–V6, on admission. The other two patients (13.3%) had diffuse T-wave inversion. Deep negative T waves were also seen during the clinical course of recovery. Although transient small Q waves were recorded in V1, V2, and V3 leads in one patient (6.7%), they disappeared 2 months after the onset. A markedly prolonged QTc interval (median, 508 ms; range 501–538 ms) was observed in nine (60.0%) patients on admission. The other two patients (13.3%) had diffuse T-wave inversion. Deep negative T waves were also seen on admission. The other two patients (13.3%) had diffuse T-wave inversion. Deep negative T waves were also seen during the clinical course of recovery. Although transient small Q waves were recorded in V1, V2, and V3 leads in one patient (6.7%), they disappeared 2 months after the onset. A markedly prolonged QTc interval (median, 508 ms; range 501–538 ms) was observed in nine (60.0%) patients within 48 h after the onset of symptoms. These electrocardiographic abnormalities were usually sustained at discharge, whereas the QTc interval normalized within 1 or 2 days in all patients.

**Echocardiography**

All patients had a similar contractile pattern, with preserved basal function, and apical akinesis or dyskinesis on admission. These left ventricular wall motion abnormalities disappeared within 11 ± 4 days of admission. The mean left ventricular ejection fraction on the initial echocardiography was 47.7 ± 6.6% and improved to 71.0 ± 7.1% (P < 0.05) by the time of discharge (21 ± 11 days). No patient had a visible left ventricular thrombus or an intraventricular obstruction during the clinical course.

**Laboratory tests**

Table 2 presents the peak and serial values found on laboratory tests. The peak CK and CK-MB were 338 ± 299 and 32 ± 30 IU/L, respectively. Elevated levels of troponin T (>0.10 ng/mL) and plasma BNP (>18 pg/mL) were observed in 13 patients (86.7%). Plasma concentrations of noradrenaline increased in all patients, whereas epinephrine increased in only six patients (40.0%). Peak plasma levels of norepinephrine and epinephrine were 744 ± 452 and 140 ± 166 pg/mL, respectively. Both of these levels showed peak values on hospital day 1 and decreased from one-third to one-half of the peak values during the hospital stay (7 ± 1 days). The serum level of D-dimer was elevated in nine patients (60.0%) and reached peak values 5 ± 1 days after the onset of symptoms. There was no statistically
significant rise in viral antibody titres in all patients through the observation period.

**Angiographic findings**

The angiographic results during the acute phase are presented in Table 3. Coronary angiography revealed neither significant stenosis nor the slow-flow phenomenon in any of the 14 patients. In three patients, intravascular ultrasound found no visible plaque rupture or vulnerable plaque in the left anterior descending coronary artery. Coronary spasm was induced in three of six patients (50.0%), epicardial single coronary spasm in two of six patients (33.3%), and multivessel coronary spasm in one of six patients (16.7%). In both patients with single coronary spasm, the spasm occurred at the site of the left anterior descending coronary artery, which was not sufficiently well developed to supply a large left ventricular territory. Left ventriculography during the acute phase revealed balloon-like left ventricular wall motion abnormalities at the apex, with hypercontraction of the basal segment of the ventricle in all patients studied (Figure 1). The initial left ventricular ejection fraction, cardiac output, and pulmonary capillary wedge pressure were 43.0 ± 8.0%, 4.4 ± 1.2 L/min, and 19.9 ± 7.5 mmHg, respectively. Two patients (14.3%) had an intraventricular pressure gradient >30.0 mmHg in the acute period. All four patients who underwent follow-up coronary angiography during the chronic phase (32 ± 6 days) demonstrated normal left ventricle wall motion, and the left ventricular ejection fraction also improved significantly to 76.7 ± 1.7% (P < 0.05).

**Endomyocardial biopsy**

Among nine patients who underwent an endomyocardial biopsy, four patients (44.4%) had interstitial myocardial fibrosis, three patients (33.3%) had mononuclear cell infiltration, and four patients (44.4%) had contraction-band necrosis by microscopic examination. None of the nine patients had significant inflammatory infiltrates or necrosis of myocytes (Figure 2).

**Positron emission tomography and single-photon emission computed tomography images**

Both PET and SPECT images of patients with tako-tsubo cardiomyopathy are shown in Figure 3. An early perfusion image demonstrated decreased ²⁰¹Tl uptake in a small area of the apex in three patients (30.0%; n = 10) without positive results on the coronary spasm provocation test. The defect images were in areas without angiographic obstructive epicardial coronary stenosis. A follow-up SPECT study was obtained in one patient 3 months after the onset of symptoms, and the apical abnormality returned to normal. On the other hand, out of eight patients, seven patients revealed severely and diffusely reduced F-18 FDG uptake in a large area where the defect pattern could not be explained by a single coronary artery distribution. Of these seven patients, six exhibited left ventricular dysfunction on echocardiography undertaken at the same time as PET with F-18 FDG. F-18 FDG PET images taken at the latest time (19 days) after the onset still showed reduced uptake. Echocardiography at that time also demonstrated left ventricular dysfunction. In addition, the extent of the metabolic defect was much larger and more severe than the perfusion defect with ²⁰¹Tl in all seven patients. None of the patients underwent serial PET studies during the observation period.

**Discussion**

Our observational study showed the following: (i) 80 % of all subjects experienced triggering emotional or physical

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**Table 3** Results of cardiac catheterization in the acute phase

| Significant stenosis in epicardial coronary artery | None |
| Slow-flow phenomenon | None |
| Positive provocation test with Ach (n = 6) | 3 (50.0%) |
| LVEF (%) | 43.0 ± 8.0 |
| Pressure gradient in LV (>30 mmHg) | 2 (14.3%) |
| PCWP (mmHg) | 19.9 ± 7.5 |
| CO (L/min) | 4.4 ± 1.2 |

Values are number of patients (%) or mean ± SD (n = 14).

Ach, acetylcholine; CO, cardiac output; LV, left ventricle; LVEF, left ventricular ejection fraction; PCWP, pulmonary capillary wedge pressure.
stress before the onset of this syndrome, (ii) plasma concentrations of norepinephrine increased in all patients, whereas epinephrine increased in only six patients (40.0%), (iii) endomyocardial biopsy specimens showed that four patients (44.4%) had contraction-band necrosis and three patients (33.3%) had mononuclear cell infiltration by microscopic examination ($n=9$), (iv) F-18 FDG PET images revealed severely reduced uptake of the apex, despite slightly reduced uptake of $^{201}$Tl in the concordant lesion ($n=7$), (v) the D-dimer values were subsequently elevated in nine patients (60.0%) and peaked about 5 days after the onset of symptoms, possibly as the manifestation of an epiphenomenon of microvascular injury, and (vi) multi-vessel coronary spasm was provoked in only one patient (16.7%; $n=6$).

Tako-tsubo cardiomyopathy is characterized by reversible left ventricular apical wall motion abnormalities with chest symptoms and electrocardiographic changes and relatively minor myocardial enzymatic release, which mimics acute coronary syndrome in patients without angiographic stenosis in the epicardial coronary artery.$^{11}$ Several lines of evidence suggest that supraphysiologic levels of plasma catecholamines induced by emotional or physical stress may play a central role in the development of this condition.$^{12,13}$ Since supraphysiologic levels of plasma catecholamine have several deleterious effects on myocytes, the pathogenesis of tako-tsubo cardiomyopathy may be multifactorial, similar to catecholamine-induced cardiomyopathy$^{14}$ such as pheochromocytoma$^{15}$ and sub-arachnoid haemorrhage$^{16}$.

Direct catecholamine injury to myocytes or myocardial metabolism predominantly accounts for the underlying pathophysiologic mechanism underlying tako-tsubo cardiomyopathy. Elevated catecholamine levels decrease the viability of myocytes through cyclic AMP-mediated calcium overload.$^{17}$ Catecholamines are also a potential source of oxygen-derived free radicals and, in animal models, cause myocyte injury that is attenuated by antioxidants.$^{18}$ Free radicals can interfere with sodium and calcium transporters, possibly resulting in myocyte dysfunction through increased trans-sarcolemmal calcium influx and cellular calcium overload.$^{19}$ Furthermore, catecholamines have also been associated with contraction-band necrosis and an interstitial mononuclear inflammatory response. Contraction-band necrosis has been described in clinical states of catecholamine excess. In our patients, the biopsy findings were consistent with the presence of an elevated catecholamine
state; three of nine patients had mononuclear inflammatory infiltrates and four patients had contraction-band necrosis. F-18 FDG is an analogue of glucose allowing non-invasive evaluation of glucose metabolism. F-18 FDG is usually transported into the cell through the glucose transporter protein (GLUT) at the cell membrane, depending on the concentration gradient of glucose from the outside to the inside of the cell. In the cell, F-18 FDG is phosphorylated to FDG-6-phosphate by hexokinase and ATP, a rate-limiting step in glycolysis. FDG-6-phosphate is not metabolized further in the glycolytic pathway, so FDG-6-phosphate remains trapped inside the cell, in a process called ‘metabolic trapping’. In our study, seven of eight patients with tako-tsubo cardiomyopathy had reduced uptake of F-18 FDG on the PET image, whereas a normal or slight defect involving the distal anterior and apical wall was on the 201Tl image. Our current study extends previous reports that the uptake of F-18 FDG was markedly reduced at the apex relative to perfusion in two patients with tako-tsubo cardiomyopathy during the acute phase. Although the precise mechanism for this reduced glucose uptake in tako-tsubo cardiomyopathy remains unclear, one possible explanation for this phenomenon is, at least in part, a metabolic disorder in the myocardium subsequent to a catecholamine surge induced by sudden stress may play an important role in the pathogenesis of this condition. In isolated rat heart, alpha-1 adrenoreceptor stimulation by plasma norepinephrine may play a role in the ischaemia-mediated increase in glucose transporter trafficking, leading to stimulation of F-18 FDG uptake; nevertheless, beta adrenergic activation does not participate in this signalling pathway. Another study showed that high-dose catecholamines possibly depress glucose uptake in rat heart in vivo, especially with respect to beta receptor stimulation. In addition, it has been reported that beta adrenergic receptor density in the apical myocardium is greater than that at the base. Hyperdense beta receptors in the apex may cause a relatively different enhancement in the responsiveness to transient catecholamine stimulation in myocytes. Hence, this biased localization of beta receptors may account for the pathophysiologic link between a transient catecholamine surge and the reduced uptake of F-18 FDG on the PET image at the left ventricular apex in patients with tako-tsubo cardiomyopathy.

The elevated values of D-dimer are indicative of the production and degradation of fibrin, thereby reflecting turnover of the coagulation system. A disturbed microcirculation may result from increased activation of coagulation and fibrin turnover, thus demonstrating intravascular fibrin generation. Norepinephrine elicits thrombosis, and the vasomotor reaction by alpha-1 adrenergic receptor stimulation precedes increased fibrinogen consumption. Epinephrine also causes an increase in fibrinogen concentrations and platelet activity. Formation and dissolution of fibrin are key events in haemostasis. Increased sympathetic tone from mental stress possibly causes vasoconstriction and coagulation activation mediated by supraphysiologic levels of plasma catecholamine, leading to subsequent microvascular dysfunction. In addition, Elesber et al. suggested that catecholamine-mediated endothelial stunning may be responsible for the microvascular dysfunction, and the severity of the perfusion defect in tako-tsubo cardiomyopathy correlates with the extent of myocardial injury. In our study, it was found that two of three patients with reduced F-18 FDG and 201Tl uptake showed higher peak levels of troponin T (0.79 ± 0.68 ng/mL) than those in the other patients studied, which is concordant with an earlier report. The previous observations reported that 43% of patients with tako-tsubo cardiomyopathy had multivessel coronary spasm on provocative testing, and electrocardiographic evidence of ST-segment elevation was common at the time of presentation. In our study, however, only one patient had angiographic evidence of multivessel coronary spasm. It is unlikely that multivessel coronary vasoconstriction and microvascular spasm may contribute to the onset of tako-tsubo cardiomyopathy. Ibanez et al. showed the pathophysiology of tako-tsubo cardiomyopathy to be the presence of a ruptured plaque in the middle portion of a well-developed left anterior descending coronary artery; however, no patient with a well-developed left anterior descending coronary artery was found in our study.

Limitations

Our observational study has several limitations. First, this was not a large-scale prospective study because of the rarity of the disease. Secondly, elevated plasma catecholamine levels may be an epiphenomenon or a secondary response in patients with tako-tsubo cardiomyopathy, rather than the root cause. Thirdly, the reason for its predilection in the elderly and in females remains unclear. Finally, we did not investigate variant forms of tako-tsubo cardiomyopathy, such as inverted tako-tsubo and mid-ventricular ballooning cardiomyopathy. Further investigation is required into the pathophysiologic mechanism of these variant forms.

Conclusion

In conclusion, a unique pattern of transient myocardial dysfunction can occur after severe emotional or physical stress, which may induce abnormal activation of adreceptors and catecholamine-induced myocardial damage. Although our data suggest that a glucose metabolic disorder in the myocardium may be a causative mechanism of tako-tsubo cardiomyopathy, a more complete understanding of the pathogenesis of this syndrome awaits further research.

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