Increased Incidence of Transient Left Ventricular Apical Ballooning (So-Called ‘Takotsubo’ Cardiomyopathy) After the Mid-Niigata Prefecture Earthquake

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Background On October 23, 2004, a major earthquake, which registered 6.8 on the Richter scale, occurred in Niigata Prefecture in Japan. Emotional stress is important as a trigger of transient left ventricular apical ballooning (so-called ‘Takotsubo’ cardiomyopathy), but its incidence and clinical profile immediately after a natural disaster have not been fully elucidated.

Methods and Results ‘Takotsubo’ cardiomyopathy was diagnosed in 16 patients (1 man, 15 women, mean age 71.5 years) within 1 month after the earthquake. Of them, 13 (81%) lived in areas where the Japan Meteorological Agency seismic intensity scale registered 6 or above, and 11 (69%) developed symptoms on the day of the earthquake. The incidence of ‘Takotsubo’ cardiomyopathy 1 month after the earthquake was approximately 24-fold higher near the epicenter than that before the earthquake.

Conclusion ‘Takotsubo’ cardiomyopathy can occur on the day of the earthquake in elderly women living near the epicenter. (Circ J 2006; 70: 947–953)

Key Words: Apical ballooning; Earthquake; Emotional stress; Left ventricle; Takotsubo cardiomyopathy

On October 23, 2004, at 17.56 h, an earthquake registering 6.8 on the Richter scale occurred in Niigata Prefecture in Japan (known as the Mid-Niigata Prefecture Earthquake). The death and injury toll was 4,848 and 120,123 houses were damaged. There are several reports concerning the increased incidence of cardiovascular diseases and sudden death after an earthquake, and emotional stress is considered to precipitate such events.

Transient left ventricular (LV) apical ballooning, so-called ‘Takotsubo’ cardiomyopathy, is a unique pathological condition characterized by transient apical and midventricular akinesis of the left ventricle.1–6 It has symptoms and electrocardiographic (ECG) changes similar to those of acute coronary syndrome (ACS).1,7 Emotional or physical stress are considered to trigger ‘Takotsubo’ cardiomyopathy but its incidence and clinical profile immediately after a natural disaster are not fully understood. We reported an increased number of cases of ‘Takotsubo’ cardiomyopathy immediately after the Mid-Niigata Prefecture Earthquake8 and the purpose of the present study was to clarify the relationship between ‘Takotsubo’ cardiomyopathy and the Mid-Niigata Prefecture Earthquake, to demonstrate the clinical characteristics and investigate the geographical and temporal distribution.

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Methods

Diagnosis and Inclusion Criteria
‘Takotsubo’ cardiomyopathy was diagnosed according to the following 4 criteria.1–3 We defined the ‘acute stage’ as the period within 10 days after the onset of ‘symptoms and the subsequent period was defined as the ‘stable stage.’

1) ST-segment elevation in 2 or more leads of a 12-lead ECG in the acute stage, followed by deep inverted T waves.
2) Coronary angiogram in the acute stage shows an absence of significant stenosis or obstruction of the epicardial coronary arteries.
3) Wall motion abnormality, including the LV apex, demonstrated by echocardiography or left ventriculography in the acute stage improves in the stable stage.
4) Cerebrovascular disease, pheochromocytoma, and myocarditis are ruled out.

Patients with ‘Takotsubo’ cardiomyopathy that developed within 1 month after the Mid-Niigata Prefecture Earthquake were included in this study.

Study Design
Niigata Prefecture is composed of 3 districts: the northeastern, central (mid-Niigata district), and southwestern areas. The epicenter of the earthquake was in the mid-Niigata district (Fig 1) and Nagaoka City is located about 20 km from the epicenter.

The Japan Meteorological Agency (JMA) seismic intensity scale measures seismic intensity is classified on a 10-grade scale9 (ie, 0 is minimal intensity followed by 1, 2, 3, 4, 5– (lower), 5+ (upper), 6– (lower), 6+ (upper), and 7). Grade 6– (lower), which corresponds to the Modified
Mercalli Intensity scale of IX or X in Western countries,10,11 causes collapse of less earthquake-resistant houses and damages the walls and pillars of highly earthquake-resistant houses, and gas pipes and/or water mains are damaged. Grade 7, which corresponds to the Modified Mercalli Intensity scale of XI or XII, is the maximal intensity imaginable and even highly earthquake-resistant buildings may be severely damaged and electrical services, gas services and water services are interrupted. The seismic intensity in each area of Niigata Prefecture was reported on the seismic intensity distribution map drawn up by JMA.12

The number of cases ‘Takotsubo’ cardiomyopathy that developed within 1 month after the Mid-Niigata Prefecture Earthquake and the clinical profiles were investigated in all medical institutions in Niigata Prefecture in which cardiac catheterization is performed. Patients were asked where they were when the earthquake occurred and the geographic relationship between seismic intensity and the occurrence of ‘Takotsubo’ cardiomyopathy was investigated using the distribution map published by JMA.

To investigate whether the incidence of ‘Takotsubo’ cardiomyopathy increased near the epicenter, the number of patients within 1 month after the earthquake at the 3 hospitals in mid-Niigata district that deal with most of the emergency care for cardiovascular disease was compared with that before the earthquake and the clinical profiles of the patients before and after the earthquake were also compared.

Examinations and Cardiac Catheterization
Serial 12-lead ECGs were recorded on admission and subsequent days. Serial creatine kinase (CK) measurements were performed. Evaluation of serum troponin T and measurement of the plasma concentration of brain natriuretic peptide (BNP) were performed within 24 h of admission. All patients underwent transthoracic echocardiography on admission followed by serial studies during hospitalization. LV wall motion, especially in the apical segment, was assessed.13

Cardiac catheterization, including coronary angiography, was performed in the acute and the stable stage. Coronary artery disease was diagnosed when the coronary angiogram revealed 75% or more stenosis of a coronary artery. A coronary spasm provocation test with ergonovine administration was performed in some patients. The left ventriculogram was evaluated according to the classification established by the American Heart Association. Particular attention was paid to the apex of the left ventricle, and abnormal wall motion was defined as akinesis, dyskinesis, or aneurysmal. Written informed consent was given by all subjects in this study.

Statistical Analysis
Data are expressed as mean±SD. Differences between all variables were analyzed using the Student’s t-test. Differences between categorical variables were analyzed using the chi-square test. A p-value <0.05 was considered significant.

Results
Clinical Profile of Post-Earthquake Cases of ‘Takotsubo’ Cardiomyopathy (Table 1)
In total, 25 patients were suspected to have developed ‘Takotsubo’ cardiomyopathy within 1 month of the earthquake and of them 16 underwent coronary angiography in the acute stage and were evaluated in this study. There was 1 man and 15 women, and their ages ranged from 49 years to 86 years (mean age: 71.5±9.4 years). None of the patients had a past history of ischemic heart disease. The interval between the onset of symptoms and admission to hospital was 0–10 days (mean: 5.1 days). The initial symptom was chest pain and a feeling of breathlessness in 15 patients and general malaise in the other patient. No patient had antecedent symptoms of the common cold.

The 12-lead ECG on admission revealed ST-segment elevation in 9 patients (56%) and deep inverted T waves in all 16 patients. The serum level of troponin-T was determined in 14 patients, and was elevated in 8 (57%). The peak CK level ranged from 76 to 655 IU/L (mean: 265±206 IU/L) with the exception of 1 patient who also had a severe thermal injury and 2-fold elevation above normal in 5 patients.
The BNP level was determined in 8 patients, and was high in all of them (100%; range: 92–662 pg/ml, mean: 394±189 pg/ml). Apical wall motion abnormality of the left ventricle was detected by echocardiography in all 16 patients within 24 h of admission, and improved in all patients by the time of discharge.

Cardiac catheterization was performed in 16 patients in the acute stage (0–10 days after the onset of symptoms; mean: 5.3 days after the onset). Left ventriculography was done in the acute stage in 13 of 16 patients and showed LV apical ballooning in all 13 patients (Fig 2). The LV ejection fraction (LVEF) ranged from 35% to 77%, and the mean value was 59.0±11.5%.

In the stable stage, repeated cardiac catheterization was performed in 5 patients (16–26 days after the onset of symptoms; mean: 23 days after the onset). Apical and mid-ventricular wall motion had improved or resolved in all 5 patients and the LVEF had increased significantly (49.4±4.3% in the acute stage vs 66.6±3.6% in the stable stage, p<0.01) (Fig 3). A coronary spasm provocation test was performed in the acute or stable stage in 6 patients, but vasospasm was not induced in any of them.

Heart failure was diagnosed in 6 patients during their hospital stay, but it improved in response to medical treatment, and no mechanical assistance, such as intraaortic balloon pumping, was needed. None of the patients developed a fatal arrhythmia such as sustained ventricular tachycardia or ventricular fibrillation. All patients were discharged from the hospital without support and had a favorable outcome.

Table 1 Clinical Characteristics of 16 Patients With ‘Takotsubo’ Cardiomyopathy After the Earthquake

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>Female patients</td>
<td>15/16</td>
<td>94%</td>
</tr>
<tr>
<td>Age (years)</td>
<td>71.5±9.4</td>
<td></td>
</tr>
<tr>
<td>History of coronary artery disease</td>
<td>0/16</td>
<td>0%</td>
</tr>
<tr>
<td>Interval between onset of symptoms and admission (days)</td>
<td>5.1±3.5</td>
<td></td>
</tr>
<tr>
<td>ST elevation</td>
<td>9/16</td>
<td>56%</td>
</tr>
<tr>
<td>Deep inverted T wave</td>
<td>16/16</td>
<td>100%</td>
</tr>
<tr>
<td>Positive serum troponin T on admission</td>
<td>8/14</td>
<td>57%</td>
</tr>
<tr>
<td>Peak CK (IU/L)</td>
<td>265±206</td>
<td></td>
</tr>
<tr>
<td>BNP on admission (pg/ml)</td>
<td>394±189</td>
<td></td>
</tr>
<tr>
<td>Abnormal wall motion of left ventricular apex on echocardiography or LVG on admission</td>
<td>16/16</td>
<td>100%</td>
</tr>
<tr>
<td>Normal coronary angiogram</td>
<td>16/16</td>
<td>100%</td>
</tr>
<tr>
<td>Positive coronary spasm provocation test</td>
<td>0/6</td>
<td>0%</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>59.0±11.5</td>
<td></td>
</tr>
<tr>
<td>Interval between onset of symptoms and LVG (days)</td>
<td>5.4±3.4</td>
<td></td>
</tr>
<tr>
<td>Alive</td>
<td>16/16</td>
<td>100%</td>
</tr>
</tbody>
</table>

CK, creatine kinase; BNP, brain natriuretic peptide; LVG, left ventriculography; LVEF, left ventricular ejection fraction.

Geographical and Temporal Distribution of Post-Earthquake Cases of ‘Takotsubo’ Cardiomyopathy

Fig 4 shows the seismic intensity distribution map for Niigata Prefecture and the residences of the patients at the time of the earthquake. The JMA seismic intensity scale in a considerable area of mid-Niigata district was Grade 6 or more. Grade 6 in Nagaoka City and Grade 7 at the epicenter. The residences of 15 (94%) of the 16 patients were in mid-Niigata district near the epicenter. The residences of
13 patients (81%) were in areas with a JMA seismic intensity scale of 6 or more, 2 patients lived in areas with an intensity scale of 5, and another patient lived in an area with a seismic intensity scale of 4. Thus, most of the patients lived in areas with a JMA seismic intensity scale greater than 6.

Fig 5 shows the number of patients according to the day of onset of ‘Takotsubo’ cardiomyopathy. The mean interval between the earthquake and the onset of symptoms was 2.5 days (0–18 days), and 11 (69%) of the 16 patients developed symptoms on the day of the earthquake.

**Incidence of ‘Takotsubo’ Cardiomyopathy After the Earthquake in Mid-Niigata District**

The annual number of cases of ‘Takotsubo’ cardiomyopathy at the 3 hospitals in mid-Niigata district is shown in Fig 6. The first case of ‘Takotsubo’ cardiomyopathy was admitted in 2000, and a total of 20 patients were diagnosed prior to the earthquake; 18 of the 20 patients were examined between January 2002 to September 2004, giving a mean number of patients per month of 0.55. In contrast, 13 patients were examined within 1 month after the earthquake, an incidence approximately 24-fold higher than before the earthquake.

**Comparison of the Clinical Profiles of ‘Takotsubo’ Cardiomyopathy Before and After the Earthquake**

The clinical profiles of the patients at the 3 hospitals in mid-Niigata district before and after the earthquake are summarized in Table 2. The mean interval between the onset of symptoms and admission to hospital was longer in patients after the earthquake than for those before it (0.6±0.7 days before vs 5.4±3.5 days after, p<0.01). Consequently, cardiac catheterization in the acute stage was delayed in patients after the earthquake (0.7±0.8 days before vs 5.4±3.5 days after, p<0.01). The LVEF in the acute stage tended to be higher in the patients admitted after the earthquake than in those before it, but was not significant. The other clinical findings of the patients before and after the earthquake did not differ.

**Discussion**

**Characteristics of ‘Takotsubo’ Cardiomyopathy and Its Relation to the Mid-Niigata Prefecture Earthquake**

The occurrence of ‘Takotsubo’ cardiomyopathy con-
verged in the mid-Niigata district; that is, near the epicenter of the earthquake. The geographic relationship between the seismic intensity distribution map and the residences of the patients clearly demonstrates the importance of the seismic intensity in the occurrence of ‘Takotsubo’ cardiomyopathy. A similar geographical feature has been reported in other illness, such as sudden death and cerebrovascular stroke, that occur after a natural disaster.10,14 A JMA seismic intensity scale of greater than 6, which corresponds to the Modified Mercalli Intensity Scale of IX or more, was a predisposing factor for the occurrence of ‘Takotsubo’ cardiomyopathy after the earthquake. The temporal distribution of ‘Takotsubo’ cardiomyopathy after the earthquake (69% of patients developed symptoms on the day of the earthquake) was similar to that reported for the occurrence of sudden cardiac death after an earthquake14 and acute myocardial infarction after the Gulf War.15 Furthermore, the number of patients treated in the hospital nearest to the

![Graph showing number of patients per month before and after the earthquake]
epicenter increased 24-fold compared with before the earthquake. These findings demonstrate that a major earthquake is a factor in the development of ‘Takotsubo’ cardiomyopathy.

Emotional Stress as a Trigger of ‘Takotsubo’ Cardiomyopathy

There have been many reports describing emotional stress as the predisposing factor of ‘Takotsubo’ cardiomyopathy and that endogenous catecholamine plays an important role.\(^1\)\(^-\)\(^6\)\(^,\)\(^16\) Enhanced sympathetic activity was demonstrated by 24-h ECG recordings in patients undergoing Holter analysis during an earthquake.\(^7\) Emotional stress can be identified in each patient on an individual basis with ‘Takotsubo’ cardiomyopathy;\(^4\)\(^-\)\(^6\) but it is unclear whether a common emotional stress, such as a natural disaster, triggers ‘Takotsubo’ cardiomyopathy in the general population. The occurrence of ‘Takotsubo’ cardiomyopathy was most frequent on the day of the earthquake (Fig 5), when many people near the epicenter were put under sudden and unexpected emotional stress. Our report confirms for the first time that the emotional stress caused by a natural disaster can trigger an outbreak of ‘Takotsubo’ cardiomyopathy.

ACS and ‘Takotsubo’ Cardiomyopathy After the Earthquake

The incidence of ACS increases after natural disasters in Western countries and in Japan.\(^18\)\(^-\)\(^21\) In contrast to ACS, ‘Takotsubo’ cardiomyopathy has characteristic clinical findings, such as female predominance, infrequent history of coronary artery disease, and relatively favorable outcome.\(^1\)\(^-\)\(^6\) However, in the acute stage it is difficult to definitively differentiate ‘Takotsubo’ cardiomyopathy from ACS by 12-lead ECG or other non-invasive methods. The results of coronary angiography were not reported in 2 previous studies\(^20\)\(^,\)\(^21\) and in the others a small number of patients underwent coronary angiography for a diagnosis of acute myocardial infarction after an earthquake, but some of them were reported to have no significant stenosis.\(^18\)\(^,\)\(^19\) Those cases may have been ‘Takotsubo’ cardiomyopathy.

‘Takotsubo’ Cardiomyopathy as a Cause of Sudden Death After the Earthquake

An earthquake was reported to be a significant trigger of sudden cardiac death\(^14\) and indeed, there was an increased incidence of cardiac death after the Mid-Niigata Prefecture Earthquake.\(^8\) It is unknown whether ‘Takotsubo’ cardiomyopathy was a predisposing cause, although there are reports of a case associated with fatal arrhythmia\(^22\) and a death from cardiac rupture.\(^23\) The outcome of ‘Takotsubo’ cardiomyopathy is generally favorable and none of the present patients developed sustained ventricular tachycardia or ventricular fibrillation. Further study is needed to determine whether a natural disaster such as the earthquake can cause serious ‘Takotsubo’ cardiomyopathy leading to sudden death.

Clinical Significance

Clinically, the differential diagnosis of ‘Takotsubo’ cardiomyopathy from ACS is very important because transvenous thrombolytic therapy is not only unnecessary in ‘Takotsubo’ cardiomyopathy, but can be hazardous. Therefore, when ACS is suspected at the time of major earthquakes, ‘Takotsubo’ cardiomyopathy must be taken into consideration, particularly in elderly females whose symptoms develop on the day of the earthquake.

Study Limitations

We evaluated 16 patients whose coronary angiogram showed no significant stenosis in the acute stage. ‘Takotsubo’ cardiomyopathy was suspected in other patients who were not included in this study because coronary angiography was not performed in the acute stage. The true incidence of ‘Takotsubo’ cardiomyopathy after the earthquake might be higher than that reported in this study.

The mean interval between the onset of symptoms and cardiac catheterization was relatively long because of disordered transportation systems and some damage to medical institutions near the epicenter especially immediately after the earthquake. Patients with ‘Takotsubo’ cardiomyopathy frequently show a rapid improvement in the wall motion abnormality within several days, and the relatively high LVEF in patients after the earthquake would be related to the delay in hospitalization and cardiac catheterization. The coronary artery might be normal in the remote phase in a patient with ACS, because of spontaneous recanalization of the obstructed coronary artery, but the incidence of that is rare.\(^3\) All patients showed typical ECG changes, only slightly elevated cardiac enzymes, except for the 1 patient with thermal injury, and rapid improvement of the LV wall motion, all of which is consistent with ‘Takotsubo’ cardiomyopathy. Furthermore, the other parameters of the clinical profiles of the patients before and after the earthquake were not different.

Conclusion

A considerable number of cases of ‘Takotsubo’ cardiomyopathy occurred after the Mid-Niigata Prefecture Earthquake, mainly in relatively elderly women living near the epicenter of the earthquake who developed symptoms on the day of the earthquake. It is important to differentiate ‘Takotsubo’ cardiomyopathy from ACS immediately after a natural disaster such as an earthquake.

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