Takotsubo (Ampulla) Cardiomyopathy: Guidelines for Diagnosis, and Pathognomonic Features

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Takotsubo cardiomyopathy is a recently described clinical entity characterized by acute but rapidly reversible left ventricular systolic dysfunction in the absence of atherosclerotic coronary artery disease. There is typically balloon-like asynergy of the ventricular apical region, ST elevation in multiple leads, and minimal elevation of cardiac enzymes. Pathological features of this cardiomyopathy and guidelines for diagnosis have not been fully clarified.

To clarify pathological features of Takotsubo (ampulla) cardiomyopathy, and the guideline development process, light microscopical examination was performed 9 autopsied cases, and 15 cases that underwent myocardial biopsy or aneurysmectomy (cases were from several institutes in Japan).

Results: 1) Myocardial injury was present, but the incidence was relatively low. Damage of single myocytes or aggregate of single myocytes was observed diffusely throughout the ventricles. 2) Extensive damage of single myocytes included. Lesion were dated based on the following findings: hypereosinophilia, myofibrillar degeneration and myocytolysis. 3) Dated on the following histological findings: hypereosinophilia, myofibrillar degeneration, myocytolysis, cell infiltration → fibroblasts → collagen fibers (fibrosis). 4) The fraction of damaged myocytes was significantly higher in the apical than the basal regions. There was focal myocyte injury, including hypereosinophilia of myocytes, myofibrillar degeneration (contraction band formation), myocytolysis, focal fibrosis, and cell infiltrates.

Discussion: The main pathological findings in autopsied hearts from patients with Takotsubo cardiomyopathy was injury of single myocyte that appeared as myofibrillar degeneration and its sequelae. The guideline development process was clarified.

Key words: myofibrillar degeneration, single myocyte injury

Takotsubo (ampulla) cardiomyopathy, also referred to as stress-provoked cardiomyopathy in the American Heart Association Scientific Statement1), is a recently described clinical entity. It is characterized by transient left and right ventricular dysfunction of an unknown cause. These cases display a balloon-like asynergy of the apical region. ST elevation in multiple leads and minimal elevation of levels of cardiac enzymes. The fact that Takotsubo cardiomyopathy cases have some minimal myocardial enzyme release is a clear sign of myocardial damage. These patients are usually misdiagnosed with acute myocardial infarction, but no significant luminal narrowing of the coronary arteries is found. Furthermore, ventricular function returns to normal within several weeks after the acute onset.

The Takotsubo phenomenon has been called by names such as acute reversible myocardial infarction, reversible left ventricular dysfunction, or transient myocardial dysfunction with electrocardiogram mimicking myocardial infarction2). Cases with Takotsubo phenomenon have contraction abnormalities of various sites that include apical, mid-ventricular, or basal segment (so-called inverted Takotsubo phenomenon). Recent reports suggested that 40% of patients with Takotsubo...
The clinical features of Takotsubo cardiomyopathy have been extensively documented in clinical studies, however, the pathological findings have not been clarified because the majority of the patients recover completely and only a small percentage of cases undergoes endomyocardial biopsy. Histopathological studies of autopsied hearts and the specimens of endomyocardial biopsy from patients with Takotsubo cardiomyopathy should be performed before considering the mechanism of Takotsubo cardiomyopathy. The differentiation of Takotsubo cardiomyopathy from other types of transient ventricular dysfunction is an important clinical necessity. Diagnostic guidelines for Takotsubo cardiomyopathy were established by a workshop of the Idiopathic Cardiomyopathy Research Committee sponsored by the Ministry of Health, Labour, and Welfare.

A questionnaire was mailed to investigators at 203 institutions who had made presentations on this disease at scientific meetings of the Japanese Circulation Society from November 1989 to October 2002. The questionnaires were sent and collected on January 10, 2003. Based on the results of the questionnaire, the first edition of the diagnostic guidelines for takotsubo cardiomyopathy were prepared and evaluated at the 2003 group meeting of the Research Committee. Out of 33 investigators in Japan who had published research papers on this disease, 21 responded to the request and provided their opinions. The diagnostic guideline was revised based on these opinions. The guidelines were revised

### Table 1 Guidelines for diagnosis of Takotsubo (ampulla) cardiomyopathy

<table>
<thead>
<tr>
<th>I. Definition</th>
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<tbody>
<tr>
<td>Takotsubo (ampulla) cardiomyopathy is a disease exhibiting an acute left ventricular apical ballooning of an unknown cause. In this disease, the left ventricle takes on the shape of a “takotsubo” (Japanese octopus trap). There is nearly complete resolution of the apical akinesis in the majority within several weeks. The contraction abnormality occurs mainly in the left ventricle, but involvement of the right ventricle is observed in some cases. A dynamic obstruction of the left ventricular outflow tract (pressure gradient, acceleration of blood flow, or systolic murmur) is also observed.</td>
</tr>
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</table>

**Note:** There are patients, such as those with cerebral hemorrhage or infarction, who have apical systolic ballooning similar to that in Takotsubo cardiomyopathy, but from a known cause. Such patients are diagnosed with “cerebrovascular disease with takotsubo-like myocardial dysfunction” and are differentiated from idiopathic cases.

<table>
<thead>
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<th>II. Exclusion Criteria</th>
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<tbody>
<tr>
<td>The following lesions and abnormalities from other diseases must be excluded in the diagnosis of takotsubo (ampulla) cardiomyopathy.</td>
</tr>
</tbody>
</table>

A. Significant organic stenosis or spasm of a coronary artery. In particular, acute myocardial infarction due to a lesion of the left anterior descending coronary artery that peruses an extensive territory including the left ventricular apex. (An urgent coronary angiogram is desirable for imaging during the acute stage, but coronary angiography is also necessary during the chronic stage to confirm the presence or absence of a significant stenotic lesion or lesion related to the abnormal pattern of ventricular contraction). |

B. Cerebrovascular disease |

C. Pheochromocytoma |

D. Viral or idiopathic myocarditis |

**Note:** For the exclusion of coronary artery lesions, coronary angiography is required. Takotsubo-like myocardial dysfunction could occur with diseases such as cerebrovascular disease and pheochromocytoma.

<table>
<thead>
<tr>
<th>III. References for diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Symptoms: Chest pain and dyspnea similar to those in acute coronary syndrome. Takotsubo cardiomyopathy can occur without symptoms.</td>
</tr>
</tbody>
</table>

B. Triggers: Emotional or physical stress may trigger Takotsubo cardiomyopathy, but it can also occur without any apparent trigger. |

C. Age and gender difference: Known tendency to increase in the elderly, particularly females. |

D. Ventricular morphology: Apical ballooning and its rapid improvement in the ventriculogram and echocardiogram. |

E. Electrocardiogram: ST segment elevation might be observed immediately after the onset. Thereafter, in a typical case, the T-wave becomes progressively more negative in multiple leads, and the QT interval prolongs. These changes improve gradually, but a negative T-wave might continue for several months. During the acute stage, abnormal Q-waves and changes in the QRS voltage might be observed. |

F. Cardiac biomarkers: In a typical case, there is only modest elevation of serum levels of cardiac enzymes and troponin. |

G. Myocardial radionuclide study: Abnormal findings in the myocardial scintigram are observed in some cases. |

H. Prognosis: The majority of the cases rapidly recover, but some cases suffer pulmonary edema and other sequelae or death.

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cardiomyopathy have an atypical pattern. The clinical features of Takotsubo cardiomyopathy have been extensively documented in clinical studies, however, the pathological findings have not been clarified because the majority of the patients recover completely and only a small percentage of cases undergoes endomyocardial biopsy. Histopathological studies of autopsied hearts and the specimens of endomyocardial biopsy from patients with Takotsubo cardiomyopathy should be performed before considering the mechanism of Takotsubo cardiomyopathy. The differentiation of Takotsubo cardiomyopathy from other types of transient ventricular dysfunction is an important clinical necessity. Diagnostic guidelines for Takotsubo cardiomyopathy were established by a workshop of the Idiopathic Cardiomyopathy Research Committee sponsored by the Ministry of Health, Labour, and Welfare.

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and approved at the 2004 group meeting. These guidelines outline the steps necessary for the diagnosis of Takotsubo cardiomyopathy (Table-1).

References for diagnosis

The following pathological conditions are of interest:
1. Onset with symptoms suspicious of acute myocardial infarction.
2. Apical ballooning with akinesis and basal hyperkinesis.
3. ST segment elevation in multiple electrocardiographic leads (longer duration of ST elevation than from coronary spasm), T-wave inversion (giant negative T-wave), QT prolongation, and lack of changes in reciprocal leads.
4. Slight elevation of cardiac enzymes (low values not proportional to the hypokinetic area).
5. Lack of significant coronary artery stenosis, and low provocation rate of coronary artery spasm (approximately 1/3).
6. Rapid normalization of the abnormal pattern of ventricular contraction, the electrocardiogram, cardiac enzymes and troponin, and the myocardial scintigram.
7. Higher incidence in elderly females (7 times higher than in males).
8. Triggered by emotional or physical stress (predominantly emotional stress in females and physical stress in males).
9. Presence of myocardial tissue damage. Some cases might have a ventricular aneurysm.
10. Reversible outflow tract obstruction might be observed in both ventricles.
11. Some cases may have an elevation in serum catecholamine levels.
12. The pathological conditions change and improve in response to various types of drugs: intracoronary verapamil improves coronary blood flow; intracoronary nitrordil improves ST elevation, and, intravenous propranolol or cibenzoline improves the outflow tract gradient and ST elevation.
13. The apical region is not opacified in contrast echocardiography.
14. There is an abnormality of coronary flow reserve in Doppler flow-wire studies.
15. In severe cases, respiratory failure can occur.

Pathognomonic features

To clarify the pathognomonic features of Takotsubo cardiomyopathy, 15 patients who had myocardial biopsy or aneurysmectomy, and 9 autopsied cases, collected from several institutes in Japan were studied microscopically using morphometrical methods.

Autopsied cases consisted of seven females (61–84 yrs. old) and two males (75 and 77 yrs. old) within 21 days after the onset. Trigger events were noted in 6 patients (2 cases with pneumonia and 1 case of septic shock, epinephrine injection, leg ulcer, and dyspnea).

Figure-1 shows single myocyte lesions in the left ventricle in one case. In this figure, two injured myocytes were observed (arrows). The myocardial injury did not extend to adjacent myocytes. Periodic acid Schiff reaction, x1000.

16. Death may occur from complications such as cardiac rupture.
difference in the distribution of the myocardial lesion between the cardiac base and apical region. The ratio of the damaged myocytes to the number of the myocytes comprising the ventricular wall was significantly higher in the apical segment (13.5%) than the basal segment (5.3%, p < 0.01). The ratio of damaged myocytes to the number of the myocytes comprising the ventricular wall in Takotsubo cardiomyopathy were relatively small compared to those of injured myocytes in patients with myocardial infarction. Damage was prominent in the apical inner and middle layers and in the anterior wall, posterior wall, and septum. The damage was particularly severe in the trabeculae of the anterior wall and subendocardium. These results indicate that it might be possible to determine the risk of Takotsubo cardiomyopathy MRI with delayed gadolinium enhancement.

The main pathological findings in the autopsied hearts from the patients with Takotsubo cardiomyopathy was myofibrillar degeneration and its sequelae, which resembled to the findings in case with catecholamine cardiomyopathy. Myofibrillar degeneration, also known as coagulative myocytolysis, is an easily recognizable form of cardiac injury.

Histology of the myocardium in patients with subarachnoid hemorrhage showed varying degrees of severity that ranged from eosinophilia with preservation of cross-striations to disruption of myocardial cell cytoplasm with the formation of dense eosinophilic transverse bands (myofibrillar degeneration).

Endomyocardial biopsy patients include 12 females and 3 males. Table-2 shows 15 cases of endomyocardial biopsy for which relevant institutions provided approval for microscopic examination. The cases are listed in the order of number of days from onset to biopsy.

1) Case biopsied on the day of onset (Case 2)
The patient was an 82-year-old woman who had undergone uterine myomectomy at the age of 48. She developed sudden pharyngeal discomfort. There was ST-segment elevation in leads II, III, aVF, and V2–V6. Echocardiography showed diffuse hypokinesis except in the base. Ventriculography revealed hyperkinesis of the base and balloon-like enlargement of the apex. Myocarditis was suspected and an endomyocardial biopsy was performed. Her condition improved on the 26th day of...
### Table 2: Endomyocardial biopsy cases

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Gender/Age</th>
<th>Underlying disorders</th>
<th>Trigger event</th>
<th>Symptoms</th>
<th>Day of biopsy</th>
<th>Biopsy pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F/71</td>
<td>Premature ventricular contraction, Hypertension</td>
<td>Status after sigmoid colon surgery, Dehydration, Cessation of beta blocking agent</td>
<td>Chest pain</td>
<td>1</td>
<td>Cell infiltrations, myocardial depletion</td>
</tr>
<tr>
<td>2</td>
<td>F/82</td>
<td>Neurosis</td>
<td>None</td>
<td>Anorexia, throat discomfort</td>
<td>1</td>
<td>Small round cell infiltration (including polymorphonuclear leukocytes), myocyte injury</td>
</tr>
<tr>
<td>3</td>
<td>F/64</td>
<td>Pulmonary fibrosis</td>
<td>Attempted suicide, Near drowning</td>
<td>Dyspnea</td>
<td>4</td>
<td>Small round cell infiltration</td>
</tr>
<tr>
<td>4</td>
<td>F/75</td>
<td>None</td>
<td>None</td>
<td>Dyspnea, chest discomfort</td>
<td>5</td>
<td>Myocardial depletion, slight fibrosis with lymphocyte infiltration</td>
</tr>
<tr>
<td>5</td>
<td>M/48</td>
<td>Hypertension</td>
<td>None</td>
<td>Sudden chest pain</td>
<td>5</td>
<td>Focal depletion, myocardial fibrosis</td>
</tr>
<tr>
<td>6</td>
<td>F/63</td>
<td>Angina pectoris</td>
<td>Emotional stress</td>
<td>Palpitation, Dyspnea, chest and back pain</td>
<td>10</td>
<td>Myocardial fibrosis, myocardial depletion, fibrocellular proliferation</td>
</tr>
<tr>
<td>7</td>
<td>M/69</td>
<td>None</td>
<td>Distress in the mountain</td>
<td>Pleural effusion</td>
<td>11</td>
<td>Cell-rich fibrosis, Focal depletion, small round cell infiltration</td>
</tr>
<tr>
<td>8</td>
<td>F/68</td>
<td>Pac, HT, AP, AR severe</td>
<td>None</td>
<td>Syncope, cough</td>
<td>12</td>
<td>Myocardial fibrosis with mild cell infiltrates</td>
</tr>
<tr>
<td>9</td>
<td>F/60</td>
<td>Hypertension</td>
<td>None</td>
<td>Cough, Dyspnea, preshock</td>
<td>15</td>
<td>Focal fibrosis, interstitial edema</td>
</tr>
<tr>
<td>10</td>
<td>F/59</td>
<td>Hypertension, Hyperlipidemia</td>
<td>Memorial service for her grandmother</td>
<td>Chest pain</td>
<td>17</td>
<td>Focal myocardial depletion, increase of connective tissue with cell infiltration</td>
</tr>
<tr>
<td>11</td>
<td>F/57</td>
<td>Sarcoidosis, hyperlipemia</td>
<td>Quarril with neighbour</td>
<td>Chest pain</td>
<td>20</td>
<td>Intermysial fibrosis, edema, sight cell infiltrates</td>
</tr>
<tr>
<td>12</td>
<td>F/76</td>
<td>Diabetes mellitus</td>
<td>None</td>
<td>Dyspnea</td>
<td>22</td>
<td>Myocardial depletion cell-rich, fibrosis, replacement</td>
</tr>
<tr>
<td>13</td>
<td>F/76</td>
<td>Status after mammary cancer, cataracta</td>
<td>Admission of her husband, stress from common cold</td>
<td>Chest pain</td>
<td>23</td>
<td>old perivascular fibrosis, slight cell infiltrates</td>
</tr>
<tr>
<td>14</td>
<td>M/53</td>
<td>Heavy drinker, Acute renal failure</td>
<td>Hypotension, Hemofiltration, Dopamine</td>
<td>Dyspnea</td>
<td>26</td>
<td>Patchy fibrosis, myocardial depletion, cell infiltration</td>
</tr>
<tr>
<td>15</td>
<td>F/74</td>
<td>Pulmonary tuberculosis</td>
<td>Quarril with neighbour for 6 months</td>
<td>Sudden chest pain</td>
<td>28</td>
<td>Perimyocardial fibrosis</td>
</tr>
</tbody>
</table>

This table shows 15 cases that had biopsy or myocardial resection. The data are listed according to the day of biopsy: from the 1st day to 28th day. Case 5 and case 7 had two samples. They received serial biopsy or aneurysmectomy. Six patients had no trigger event, and chest pain was absent in 7 patients. Cases in early phase (from 1st day to 4th day biopsy) showed cell infiltration, myocardial depletion, and myocardial injury. Cases in late phase (12th day or later) showed focal fibrosis.
illness. The biopsy showed a slight increase in immature connective tissue and infiltration of cells, including polymorphonuclear leukocytes.

2) Case thought to have a ventricular aneurysm (Case 7)

The patient was a 69-year-old man with no contributory medical history. He became lost in the mountains while gathering edible wild plants and was rescued 7 hours later. He experienced shortness of breath thereafter and had pleural effusion 18 days later. Coronary angiography revealed 90% occlusion in #11 and complete occlusion in peripheral #12. There was also unexplainable severe left ventricular asynergy and an apical mural thrombus. An endomyocardial biopsy showed cell-rich fibrosis. One week later, his condition improved except in the circumflex branch and apical regions. He underwent resection of a ventricular aneurysm 2.5 months later. Histologically, the ventricular aneurysms showed endocardial fibroelastosis. There was also a full-thickness loss of myocytes, leaving only a small amount of remaining myocytes in the inner layer, and fibrosis with flaccidity (Figure-3B).

3) Case with serial biopsies (Case 5)

The patient was a 48-year-old man who was taking a channel blockers for hypertension that was diagnosed in 1996. At 4 AM on September 5, 1998, he suddenly experienced chest pain that lasted 20 minutes. He developed mild chest pain at 5 PM and was admitted to the hospital at 9 PM. His white blood cell count was moderately elevated at 16,000. Electrocardiography revealed no abnormality but echocardiography revealed extensive asynergy mainly in the apex. Emergency cardiac catheterization was performed while an intravenous nitrate was administered. Coronary angiography was normal, but left ventriculography showed Takotsubo-like ballooning. The patient complained of severe chest pain during the procedure. For the first time,
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the patient showed ST-segment elevation of 6 mm in one of the precordial leads. When coronary angiography was performed again, no abnormality was observed and coronary blood flow measurement indicated a hyperdynamic state. The patient underwent conservative treatment and his symptoms improved after a few hours. A giant negative T-wave was subsequently observed, but left ventriculogram showed a tendency for improvement one month later. An endomyocardial biopsy was performed on the fifth day, and there was loss of myocytes and an increase in immature connective tissue rich in cellular elements (Figure-3C). Mature connective tissue was observed in the biopsy one month later (Figure-3D).

Dating of histological events in Takotsubo cardiomyopathy was performed based on the presence of the following feature: 1) hypereosinophilia or myofibrillar degeneration, 2) myocytolysis, 3) cell infiltration to the injured myocytes, 4) accumulation of fibroblasts, and, 5) fibrosis. The myocardial lesions were characterized mainly by individual myocytes or myocyte aggregates with increased eosinophilic staining, contraction band formation, necrosis, and rupture. The basis of the lesion was damage of individual myocytes and aggregates of these damaged myocytes. It was speculated that early cell infiltration occurs followed by changes over time, including loss of myocytes and focal fibrosis. The presence of diffuse myocardial lesions in Takotsubo cardiomyopathy suggested focal myocardial damage occurring at multiple sites throughout the ventricle.

There are a lot of assumptions about mechanisms of Takotsubo cardiomyopathy including myocarditis. The cases with biopsy-proven myocarditis mimicking Takotsubo cardiomyopathy have been reported. Furthermore, several researchers have documented the presence of myocardial edema, fibrosis, and necrosis in cases with Takotsubo cardiomyopathy using cardiac magnetic resonance imaging (CMR). However, these CMR findings in Takotsubo cardiomyopathy in which clinical suspicion for active myocarditis are lacking do not demonstrate definite evidence of active myocarditis. Edema are a common pathological phenomenon in catecholamine cardiomyopathy. Fibrosis is a fundamental component of the adverse structural remodeling of myocardium. Replacement fibrosis appears at sites of previous myocardial necrosis to preserve the structural integrity of the myocardium. It remains to be established whether CMR-defined inflammation is a direct cause of Takotsubo cardiomyopathy or a secondary phenomenon of myocardial injury.

References

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