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Review

Takotsubo cardiomyopathy, a new concept of cardiomyopathy: Clinical features and pathophysiology

Tsutomu Yoshikawa

Department of Cardiology, Sakakibara Heart Institute, 3-16-1 Asahi-cho, Fuchu 183-0003, Japan

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ABSTRACT

Takotsubo cardiomyopathy, a new concept of cardiomyopathy, is characterized by transient cardiac dysfunction, commonly triggered by physical or emotional stress. Differential diagnosis is important, since takotsubo cardiomyopathy presents similar images to those shown in acute coronary syndrome, with ST-segment elevation, T-wave inversion, QT-prolongation, and others on electrocardiogram. Typically, apical involvement with hypercontraction of basal left ventricle (apical type) is predominant, but atypical types involving basal, mid-ventricular, and right ventricular myocardium are also described. In-hospital death occurs at similar level with patients with acute coronary syndrome, but it is significantly affected by underlying diseases. This disease presents diverse cardiac complications in acute phase, such as life-threatening ventricular arrhythmias, pump failure, cardiac rupture, and systemic embolism. The pathogenic mechanism of this disease is still unclear but sympathetic hyperactivity, as well as coronary vasospasm, microcirculatory disorder, and estrogen deficiency, have been considered as one of the most likely pathogenic mechanism. Long-term prognosis is also largely unknown. Issues such as establishment of acute phase treatment, prediction of cardiac complications, and prophylactic measures against recurrence need to be further explored.

Transient cardiac dysfunction with characteristic morphology has been termed as "takotsubo cardiomyopathy", a new concept of cardiomyopathy, commonly induced by emotional or physical stress. The name is derived from the appearance of the left ventricular angiographic image shown during an attack, like an octopus trap, "takotsubo" in Japanese. Outside Japan, it is also typically called as "transient apical ballooning", "stress cardiomyopathy", or "broken heart syndrome". Although Iga et al. [49] reported a case of similar pathological conditions with pheochromocytoma in 1989, the term "takotsubo cardiomyopathy" was first described in 1990 by Sato et al. in their report. Takotsubo cardiomyopathy is closely similar to acute coronary syndrome with ST elevation and therefore differential diagnosis is crucially important in the site of emergency care. In addition, special consideration is required when takotsubo cardiomyopathy is complicated by heart failure. This review briefly describes on diagnosis and therapy of takotsubo cardiomyopathy. Since its underlying pathophysiology appears fascinating, author will summarize recent progress in the conceptual advancement.

1. Diagnostic criteria

The diagnostic criteria are advocated by both Mayo Clinic [1] and the Japanese Circulation Society [2] (Table 1). Characteristics associated with pheochromocytoma are excluded in both criteria but cerebrovascular disease is differently considered. It is excluded from the diagnostic criteria of the Japanese Circulation Society but is not listed as an exclusion criterion of Mayo Clinic. Both diagnostic criteria require the absence of significant lesion on coronary angiograms. As mentioned above, the concept of this disease was originally advocated from Japan, but the Mayo Clinic criteria for diagnosis of takotsubo cardiomyopathy have been commonly and internationally used.

Wall motion abnormalities of takotsubo cardiomyopathy are typically characterized by apical systolic dysfunction and hyperdynamic basal contraction. The occurrence of such abnormalities varies with reports but apical pattern accounts for about 80–90% of the whole. Recently, however, the cases of apical-sparing pattern of motion abnormalities commonly in mid-ventricular and basal portions have been often reported. Some reports have described the right ventricular pattern that tends to follow a serious clinical course [3].

2. Epidemiology

Most of takotsubo cardiomyopathy cases have been conventionally reported from Japan. Therefore, this disease was once estimated to be peculiar to Japan. Reports from outside of Japan have been rapidly increased since 2000 and clinical studies of many cases have appeared on wide variety of medical journals (Table 2). This disease presents pathology mimicking acute coronary syndrome and therefore the differential diagnosis of such pathology is confusable. It was reported that

E-mail address: tyoshi@shi.heart.or.jp.

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Table 1
Diagnostic criteria.

I. Mayo Clinic criteria [1]
(1) Transient hypokinesis, akinesis, or dyskinesis in the left ventricular mid segments with or without apical involvement; regional wall motion abnormalities that extend beyond a single epicardial vascular distribution; and frequently, but not always, a stressful trigger.
(2) The absence of obstructive coronary disease or angiographic evidence of acute plaque rupture.
(3) New ECG abnormalities (ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin.
(4) The absence of pheochromocytoma and myocarditis.

II. Japanese Circulation Society criteria [2]
(1) Acute left ventricular ballooning of unknown cause.
(2) The left ventricle takes on the shape of a "takotsubo" (Japanese octopus trap).
(3) Nearly complete resolution of the apical akinesis in the majority of the patients within a month.
(4) The contraction abnormality occurs mainly in the left ventricle, but the involvement of the right ventricle is observed in some cases.
(5) A dynamic obstruction of the left ventricular outflow tract is also observed.
(6) The absence of significant organic stenosis or spasm of a coronary artery, cerebrovascular disease, pheochromocytoma, viral or idiopathic myocarditis.

the occurrence of acute myocardial infarction provoked by earthquake was rapidly increased but it could be at least probably sure that some of them were considered to this disease. Actually, it was noted that half of such disease reported from Japan was found to be takotsubo cardiomyopathy [4]. One of the features of takotsubo cardiomyopathy is a predominant occurrence in elderly women. The reason is uncertain but reduction of estrogen level with menopause is noted as one of the major factors. A chronobiological pattern of this disease has been discussed in some reports. It has been described in some reports with a peak incidence of this disease in summer [5] and in the evening, which is different from myocardial infarction [6].

The most common subjective symptom is chest pain. Other less common symptoms are dyspnea, palpitations, and physical fatigue. These symptoms are commonly characterized by a preceding physical or emotional stress. Reported stressors are perioperative stresses, death of a family person, surprise party, septicemia, drug addiction, dobutamine or ergonovine stress test, lightning strike, and thyrotoxicosis. At first, abnormal stimulation of the sympathetic nervous system has been estimated to be a major mechanism, in terms of these characteristic pathological patterns.

Table 2
Major clinical studies on takotsubo cardiomyopathy.

Authors	Year	Number of patients	Main results
Elesber et al. [16]	2007	100	10% recurrence rate during 4.4 years
Sharkey et al. [46]	2010	130	In-hospital mortality rate 2%, recurrence rate 5%. All-cause mortality during follow-up higher than matched general population with most deaths occurring in the first year.
Eitel et al. [10]	2011	256	Myocardial edema (81%), inflammation (67%), and patchy late gadolinium enhancement (9%) on magnetic resonance imaging
Brinjikji et al. [17]	2012	24,701	Higher mortality in male than female (8.4% vs. 4.2%)
Sharkey et al. [6]	2012	186	Circadian pattern with a peak in the afternoon
Murakami et al. [47]	2014	107	High white blood cell count and brain natriuretic peptide level are associated with adverse in-hospital outcome
Citro et al. [48]	2014	227	LV ejection fraction, E/e′ ratio, reversible moderate to severe mitral regurgitation, age >75 years were predictors of major adverse events

3. Laboratory tests

The concentration level of plasma brain natriuretic peptide (BNP) increases in acute phase. This change is considered to reflect the ventricular wall stretch. Whereas, changes in cardiac biomarkers, such as creatinine phosphokinase and troponin T, are relatively slight than the expectation compared to the level of wall motion abnormalities. Elevation in the concentration level of the plasma catecholamine has been also reported. The elevation is more remarkable as demonstrated in patients with acute myocardial infarction and the elevation in the concentration level of epinephrine is especially remarkable [7]. Acute coronary syndrome with ST elevation is noted as one of the most typical diseases that require differential diagnosis with takotsubo cardiomyopathy. The differential diagnosis point has been suggested to be the presence of relatively remarkable elevation of the concentration level of brain natriuretic peptide (BNP) compared to troponin T (TnT). It has been considered that BNP/TnT ratio would be useful for the differential diagnosis [8].

4. Electrocardiogram

ST-segment elevation and subsequent T-wave inversion are almost always observed in precordial lead in acute phase. In some cases, these are associated with QT interval prolongation. A transient appearance of Q waves can be sometimes noted. Afterwards, inverted T wave flattens once and becomes prominent again. These phenomena are closely similar to those of acute anteroseptal myocardial infarction. As the differential diagnosis points, the absence of ST-segment elevation in V_1 and the presence of ST-segment depression in aVR (ST-segment elevation in aVR) are noted. Combination of both factors showed 91% sensitivity, 96% specificity, and 95% positive predictive accuracy in identifying this disease [9]. These electrocardiographic changes commonly normalize in several months. Characteristic T-wave inversion of takotsubo cardiomyopathy may be associated with sympathetic denervation. Large area of denervation compared to myocardial necrosis in this disease, in terms of a relatively prominent range of T-wave inversion compared to acute myocardial infarction can be estimated.

5. Ultrasonic echocardiography

In an early stage of the onset, echocardiography is needed to assess systolic dynamics and check for the presence of mitral valve insufficiency. Complication of left ventricular outflow tract stenosis is presented in 18 to 25% of patients with this disease. Anterior motion of mitral valve resulting from tethering by apical akinesis, as well as hyperdynamic basal contraction, is involved in this phenomenon. In some cases, sigmoid septum is considered to be involved in such pathology. Especially, when systolic murmur, refractory heart failure, and hypotension are presented, a possibility of this pathology should be considered.

6. Magnetic resonance and radionuclide imaging

Magnetic resonance imaging technique is helpful to assess not only a cardiac function with takotsubo cardiomyopathy but also myocardial tissue characteristics. Myocardial edema in the regions corresponding to the regions presenting systolic dysfunction is frequently detected on a T2-weighted image of this disease in acute phase. Positive delayed enhancement is detected in a few cases. However, it is still not revealed how these findings are associated with the subsequent clinical outcomes [10].

By radionuclide imaging, a thallium uptake in myocardial thallium scintigraphy was also slightly reduced [11]. Reduction of fatty acid metabolism during acute phase was also reported using ^{123}I-β-