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Review

Tako-tsubo cardiomyopathy: Clinical presentation and underlying mechanism

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ABSTRACT

Since Dr Sato at Hiroshima City Hospital first recognized and reported the concept of tako-tsubo cardiomyopathy in 1990, this disorder has become accepted worldwide as a distinct clinical entity. Tako-tsubo cardiomyopathy is an important disorder as a differential diagnosis of acute myocardial infarction. This disorder usually occurs in postmenopausal women of an advanced age, and is characterized by transient left ventricular apical wall motion abnormalities associated with emotional or physical stress. Typically, left ventricular apical wall motion abnormalities are transient and resolve during a period of days to weeks. The prognosis is generally favorable. However, several acute complications have been reported such as congestive heart failure, cardiac rupture, hypotension, left ventricular apical thrombosis, or Torsade de Pointes. Several possible mechanisms such as multivessel coronary artery spasm, coronary microvascular dysfunction, myocarditis, or catecholamine toxicity have been proposed to explain tako-tsubo cardiomyopathy, but its pathophysiology is not well understood.

Contents

Introduction

A novel cardiac syndrome exhibiting transient left ventricular apical wall motion abnormalities associated with emotional or physical stress has become accepted worldwide as a distinct clinical entity. This disorder has been widely called the tako-tsubo cardiomyopathy [1–4]. Tako-tsubo is a pot with a round bottom and narrow neck used for trapping octopuses in Japan (Fig. 1), which resembles the left ventriculogram during systole in these patients. More recently, this disorder has been called by various names based on its most important inciting factor or its angiographic image: stress-related cardiomyopathy [5] or transient left ventricular apical ballooning syndrome [6,7]. In 2006, the American Heart Association incorporated this disorder into the classification of cardiomyopathies as an acquired cardiomyopathy [8]. In this review, we will summarize the current knowledge on tako-tsubo cardiomyopathy including clinical features and potential pathophysiological mechanisms.

History of tako-tsubo cardiomyopathy

Even before 1990, several reports had shown acute and reversible left ventricular apical wall motion abnormalities after

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Fig. 1. Tako-tsubo.

虚血による細胞障害

《解 説》

1。虚血心筋の代謝異常

2。Stunned myocardium と calcium overload

1. 心筋梗塞発症時の冠循環・心筋代謝
2. 梗塞部における残存心筋の評価
3. NTG 反応性からみた心筋梗塞部の viability
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7. 冠血流改善と心筋灌流の不一致例について

臨床からみた心筋細胞障害, 科学評論社, 1990

Fig. 2. Table of contents including the first report of tako-tsubo cardiomyopathy described by Dr Sato.
Adapted from Ref. [1], with permission.

emotional or physical stress. In 1985, 6 cases of transient left ventricular apical wall motion abnormalities after non-cardiac surgery were reported in Japan [9]. In these cases, coronary angiography was not performed. In 1986, a female case of transient left ventricular apical wall motion abnormalities after her son's suicide was reported in the USA [10]. In this case, coronary angiography revealed no significant stenosis. Similar cases complicated by pheochromocytoma or subarachnoid hemorrhage were also recognized about that time [11,12]. These reports suggested several possible pathophysiological mechanisms to explain this phenomenon including myocarditis, coronary artery spasm, or focal myocytolysis due to catecholamine surge.

In 1990, Dr Sato at Hiroshima City Hospital first recognized the concept of reversible left ventricular apical wall motion abnormalities without coronary artery disease (CAD), and originally proposed the term "tako-tsubo-like left ventricular dysfunction" because the shape of left ventriculogram during systole resembled a tako-tsubo [1] (Fig. 2). In Japan, this disorder was gradually recognized through the funny name and subsequent his colleagues' reports [1–4].

After 2000, Japanese researchers introduced this disorder outside Japan with English papers, and its concept and the name "tako-tsubo cardiomyopathy" have been gradually recognized

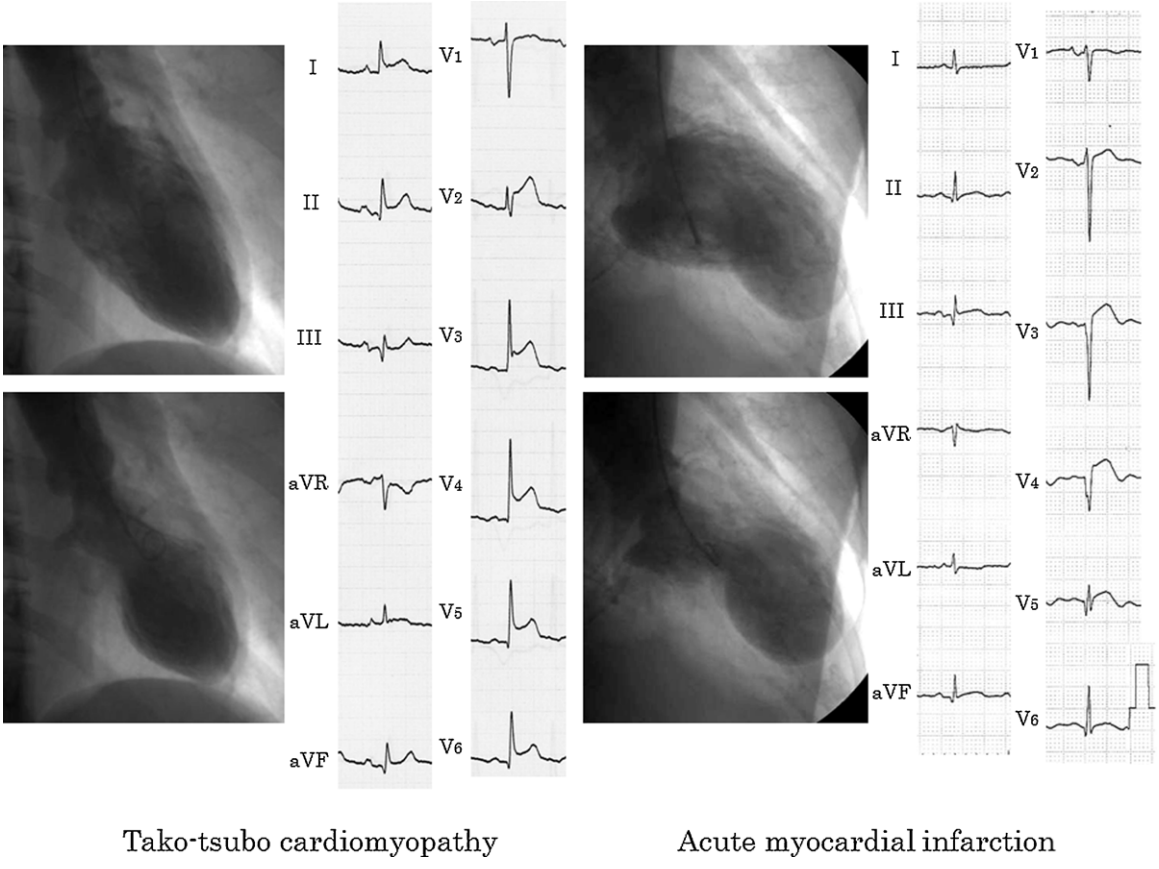

Fig. 3. Left ventriculogram and electrocardiogram in tako-tsubo cardiomyopathy (left panel) and anterior acute myocardial infarction (right panel).
Adapted from Ref. [14], with permission.

worldwide [3,6,7,13]. The number of published reports of patients with tako-tsubo cardiomyopathy has been steadily increasing during the past decade.

Diagnosis

In tako-tsubo cardiomyopathy as well as acute myocardial infarction (AMI), most patients have chest symptoms, electrocardiographic (ECG) abnormalities or left ventricular apical wall motion abnormalities during the early stage (Fig. 3) [14]. Thrombolytic agents are useful for achieving early reperfusion in patients with AMI. However, inappropriate administration of thrombolytic agents may lead to harm in patients with tako-tsubo cardiomyopathy. Therefore, it is important to obtain an early and precise diagnosis in these patients. It would be reasonable to perform coronary angiography in patients with suspected tako-tsubo cardiomyopathy during early phase if it is clinically possible. Tako-tsubo cardiomyopathy has been diagnosed classically based on angiographic findings including left ventricular apical wall motion abnormalities and the absence of obstructive CAD or acute plaque rupture. Researchers at Mayo Clinic proposed their criteria in 2004, and subsequently showed its modified version in 2008 as follows [15]: (1) transient hypokinesis, akinesis, or dyskinesis of the left ventricular mid segments with or without apical involvement; the regional wall motion abnormalities extend beyond a single epicardial vascular distribution; a stressful trigger is often, but not always present; (2) absence of obstructive CAD or angiographic evidence of acute plaque rupture; (3) new electrocardiographic abnormalities (either ST-segment elevation and/or T wave inversion) or modest elevation in cardiac troponin; and (4) absence of pheochromocytoma and myocarditis. It is required to establish worldwide consensus on the diagnostic criteria for tako-tsubo cardiomyopathy.

Clinical features

Patients' characteristics

The true prevalence of tako-tsubo cardiomyopathy remains uncertain because of its under-recognition or absence of worldwide consensus on the diagnostic criteria. In addition, some cases of tako-tsubo cardiomyopathy may have been diagnosed as aborted AMI or myocarditis in the past. However, according to recent reports from several countries including Japan, the USA, and Europe, tako-tsubo cardiomyopathy probably accounts for 1–3% of patients with suspected AMI [16,17]. Tako-tsubo cardiomyopathy usually occurs in postmenopausal women of an advanced age. Recent reviews of the published case series reveal that approximately 90% of reported cases have been women and the mean age has ranged from 58 to 75 years [3,6,7,13–19]. The most common symptom is chest pain or dyspnea which is also frequently found in AMI. Because these symptoms in tako-tsubo cardiomyopathy are not usually as serious as those in AMI, its development may be diagnosed at a later stage or overlooked. Pulmonary edema may occur, but cardiac arrest, cardiogenic shock, and serious arrhythmias are rare as an initial presentation. A unique feature of tako-tsubo cardiomyopathy is the occurrence of a preceding emotional or physical stress. An emotional stress such as an unexpected death of a relative or friend, domestic abuse, public speaking, or receiving news of serious diagnosis, and a physical stress such as asthma attack, gastric examination, or non-cardiac operation have been identified in previous cases [3,6,7,13–23]. These are commonplace events that everyone can experience in their daily life. We experienced 2 cases of tako-tsubo cardiomyopathy that were diagnosed after successful resuscitation of cardiac arrest [20]. We recently reported

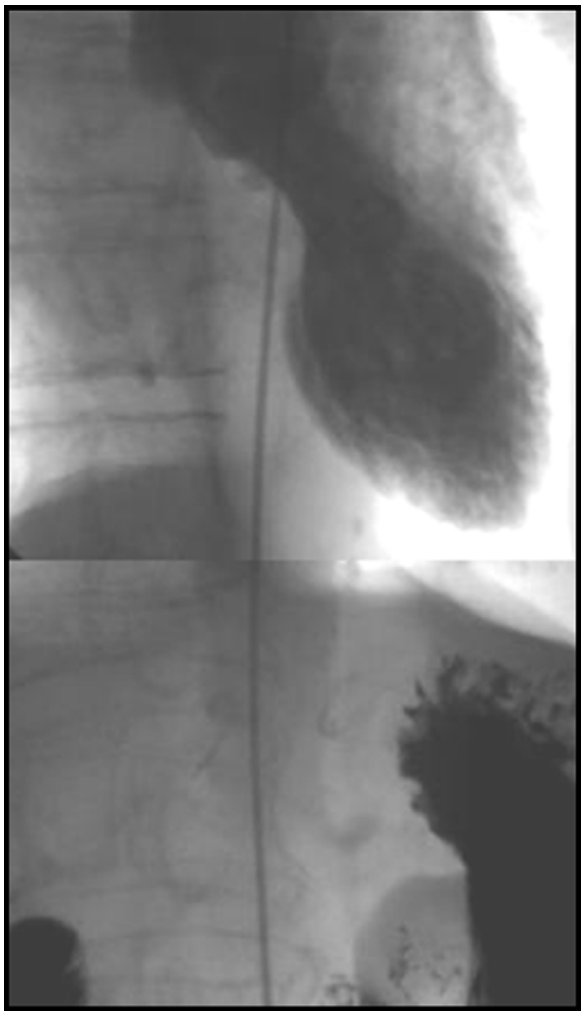

Fig. 4. Tako-tsubo cardiomyopathy after upper gastrointestinal examination. Swallowed barium was seen in the gastrointestinal tract.
Adapted from Ref. [23], with permission.

gender differences in the clinical characteristics [21]. In 10 of the 13 male patients, tako-tsubo cardiomyopathy occurred during or immediately after receiving medical examination or treatment. The incidence of in-hospital onset was significantly higher in male patients than in female patients (77% vs 17%, $p < 0.01$). Our results suggested that physical stress might be much more associated with the occurrence in male patients compared to female patients. Physicians should recognize that this disorder can occur unexpectedly during medical examination or treatment (iatrogenic tako-tsubo cardiomyopathy) [22,23] (Fig. 4).

Electrocardiogram and cardiac biomarkers

The most common abnormality on the initial ECG is ST-segment elevation or negative T wave. There is a significant variability in the frequency of these ECG abnormalities in the published reports possibly because of the variability in time from onset to recording ECG [3,6,7,13–19]. Typically, ST-segment elevation is found in precordial leads immediately after the onset. It may be seen in limb leads. Because ECG features are similar between tako-tsubo cardiomyopathy and anterior AMI, several studies have assessed ECG differences [19,24,25]. Ogura et al. reported that the absence of reciprocal changes, the absence of abnormal Q wave, and the sum of ST-segment elevation in leads V4–6 more than the

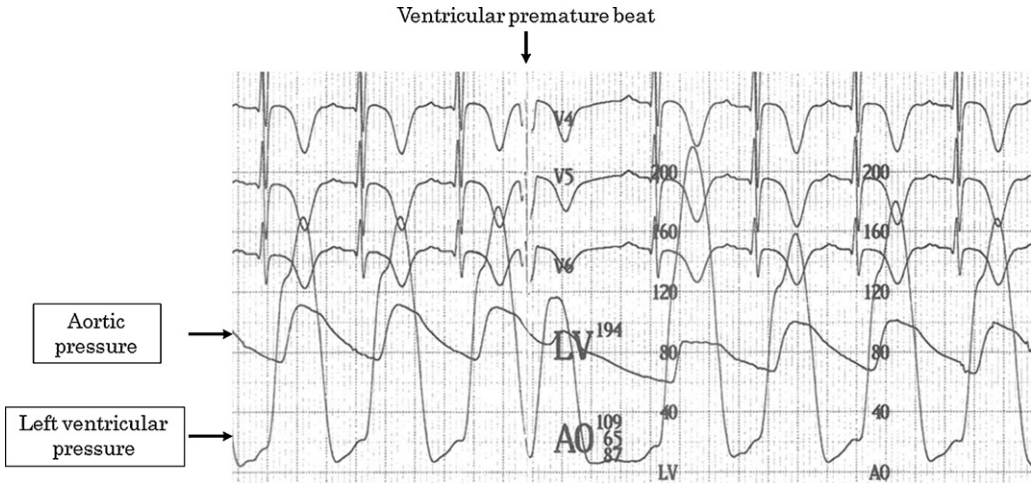

Fig. 5. Simultaneous tracings of left ventricular and central aortic pressures. Initial recording showed a peak systolic gradient of 60 mmHg. On the first sinus beat after a premature ventricular contraction, the peak systolic gradient increased to 130 mmHg.
Adapted from Ref. [31], with permission.

sum of ST-segment elevation in leads V1–3 identified tako-tsubo cardiomyopathy with a high sensitivity and specificity [19]. Kosuge et al. recently reported that the combination of the presence of ST-segment depression in lead aVR and the absence of ST-segment elevation in lead V1 also showed a high sensitivity and specificity for diagnosing tako-tsubo cardiomyopathy [24]. We reported typical time course of ECG in tako-tsubo cardiomyopathy as follows [25]. ECG shortly after the onset usually showed ST-segment elevation. Negative T wave deepened progressively to its first negative peak, which occurred at approximately 3 days. The negative T wave was shallow for several days and then deepened again, the second negative peak occurring at approximately 2 weeks. QT interval was prolonged as the T wave deepened, and shortened as the T wave became shallow. Interestingly, the time course of ECG in tako-tsubo cardiomyopathy mimicked that in reperfused AMI with minimal enzymatic release.

Serum levels of creatine kinase, creatine kinase-MB, and troponin may be normal or slightly elevated. These levels may be unexpectedly normal in spite of broad wall motion abnormalities during the early stage. Brain natriuretic peptide (BNP) or N-terminal pro-BNP, a marker of ventricular dysfunction, is usually elevated, but is not associated with a poor prognosis [26].

Cardiac catheterization

Typically, left ventriculography shows akinesis in the apical and mid portions of the left ventricular chamber extending beyond one coronary artery region, with hyperkinesis in the basal portion. The size of akinetic area varies during the early stage [27]. It remains unclear what regulates the size of akinetic area. Left ventricular wall motion abnormalities improve from basal-side to apical-side [28], and are usually resolved during a period of days to weeks. We experienced a case of tako-tsubo cardiomyopathy in which left ventricular apical wall motion abnormalities were resolved during only 41 h on left ventriculography [29]. Left ventricular outflow tract obstruction or mitral regurgitation may be found during the early stage [30–32]. In patients with left ventricular outflow tract obstruction (obstructive tako-tsubo cardiomyopathy), Brockenbrough–Braunwald–Morrow phenomenon, which is well known in hypertrophic obstructive cardiomyopathy, is observed [30,31] (Fig. 5). Acute mitral regurgitation in tako-tsubo cardiomyopathy is likely due to complex and multiple mechanisms. Nevertheless, the main factor seems to lie in the altered spatial relationship between mitral leaflets and the subvalvular apparatus, caused by the apical ballooning. In patients with severe mitral regurgitation, the shape of left ventriculogram and the resulting left atriogram during systole resembles a dumbbell (Fig. 6). Apical wall motion abnormalities or intraventricular obstruction may be also found in the right ventricle [33]. Recently, apical sparing variant of tako-tsubo cardiomyopathy has been described, occurring in a significant minority of patients with a clinical presentation similar to that of typical tako-tsubo cardiomyopathy [34]. Apical sparing variant of tako-tsubo cardiomyopathy shows limited ECG abnormalities compared to typical tako-tsubo cardiomyopathy [35] (Fig. 7). It may be difficult to obtain early and precise diagnosis of apical sparing variant of tako-tsubo cardiomyopathy by using ECG.

Most patients with tako-tsubo cardiomyopathy have angiographically normal coronary arteries or mild atherosclerosis. It is an important concept of this disorder that left ventricular apical wall motion abnormalities are not due to myocardial ischemia with coronary atherosclerosis or acute plaque rupture. However, it is probable that patients with tako-tsubo cardiomyopathy have an incidental CAD because most patients are elderly. We recently reported that incidental CAD (>75% stenosis of a major epicardial coronary artery) was found in 10% of patients with tako-tsubo cardiomyopathy [36]. In patients with CAD in the left anterior descending artery, it should be carefully judged whether the CAD is associated with left ventricular wall motion abnormalities to avoid performing unnecessary coronary intervention. We and another group have also reported that coronary blood flow is impaired in all coronary arteries, in agreement with akinetic area extending beyond one coronary artery region by using thrombolysis in myocardial infarction (TIMI) frame count [16,37].

Cardiac imaging

Myocardial single-photon emission computed tomography has shown myocardial perfusion, fatty acid metabolism, and sympathetic function in tako-tsubo cardiomyopathy [13,37,38]. Reduced uptake of technetium-99m or thallium-201 indicating decreased myocardial perfusion is found during early stage. Reduced uptake of iodine-123-beta-methyl-*p*-iodophenyl pentadecanoic acid, or ^{123}I-meta-iodobenzylguanidine is also found during the early stage. These indicate abnormal fatty acid metabolism and sympathetic denervation, respectively. The regional distribution of abnormal

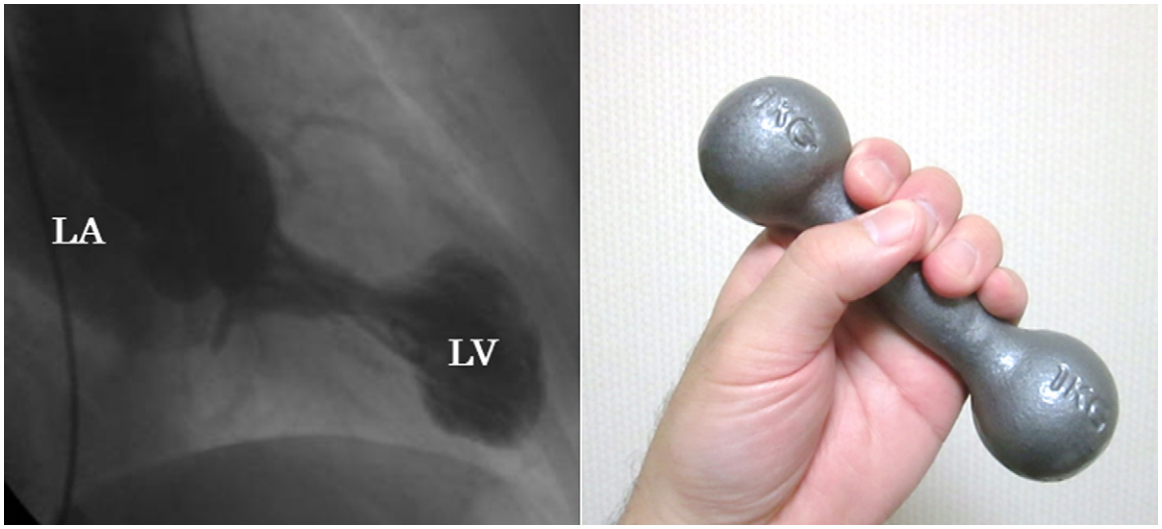

Fig. 6. Tako-tsubo cardiomyopathy complicated by severe mitral regurgitation. The shape of left ventriculogram and the resulting left atriogram during systole resembles a dumbbell. LA, left atrium; LV, left ventricle.

fatty acid metabolism or sympathetic denervation corresponds with the regional distribution of left ventricular apical wall motion abnormalities. Abnormal fatty acid metabolism and sympathetic denervation are usually sustained even after the resolution of left ventricular wall motion abnormalities. Cardiac magnetic resonance imaging has shown that late gadolinium enhancement is almost never found, but T2-weighed sequence reveals frequent high signal intensity suggesting myocardial edema. This modality seems to be useful in detecting apical thrombus or right ventricular involvement [39].

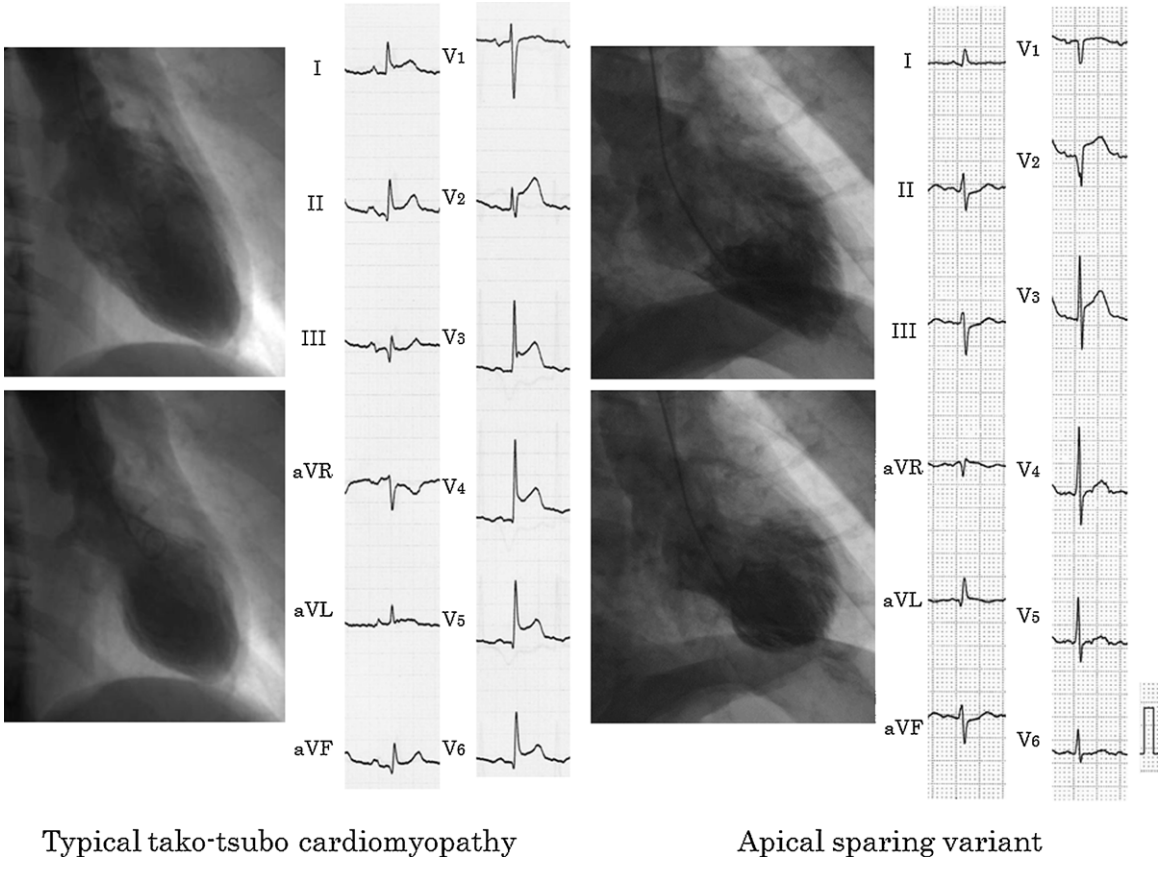

Fig. 7. Left ventriculogram and electrocardiogram in typical tako-tsubo cardiomyopathy (left panel) and apical sparing variant (right panel). Adapted from Ref. [35], with permission.

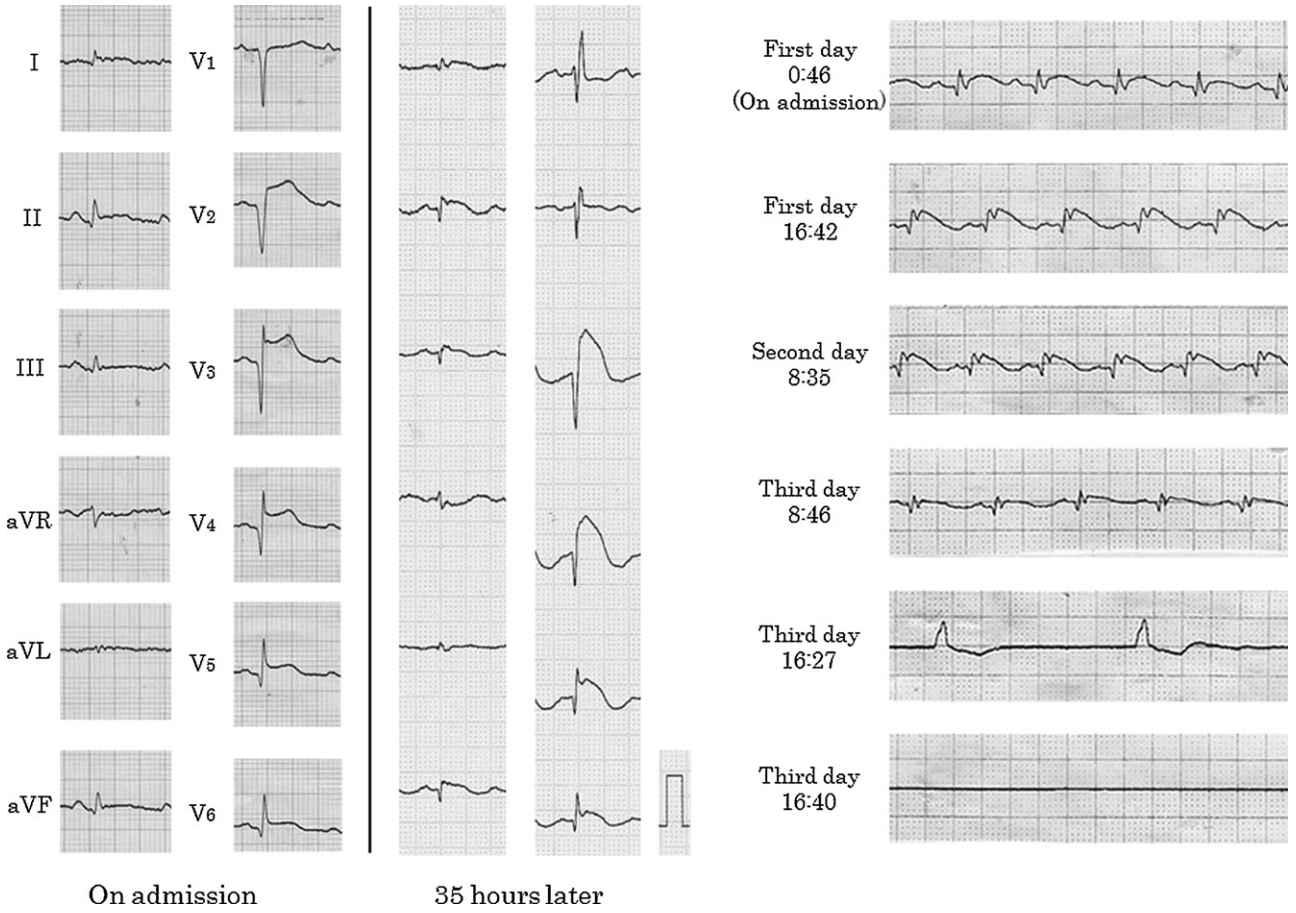

Fig. 8. Serial electrocardiogram (left panel) and telemetry monitoring (right panel) in a case of tako-tsubo cardiomyopathy complicated by cardiac rupture. Note that ST-segment elevation persists without negative T wave even on the third day.
Adapted from Ref. [42], with permission.

Prognosis, complications, and management

Typically, left ventricular apical wall motion abnormalities are transient and resolved during a period of days to weeks. The prognosis is generally favorable; reported in-hospital mortality rates range from 0% to 8% [3,6,7,13–19]. Tako-tsubo cardiomyopathy can occur in critically ill patients during hospitalization, and their outcome seems to be dependent on the underlying disease rather than tako-tsubo cardiomyopathy itself [21]. Recurrence occurs in approximately in 10% of patients [40]. Interestingly, several reports have shown that typical tako-tsubo cardiomyopathy and apical sparing variant can occur sequentially in the same patient [41]. Tako-tsubo cardiomyopathy can occur despite treatment with calcium channel blockers, nitrates, or beta-blockers, suggesting limitation of these medications to prevent tako-tsubo cardiomyopathy [29]. It is necessary to clarify the underlying pathophysiological mechanisms and reach consensus in long-term management especially in recurrent cases. Several acute complications have been reported and highlight the implications of tako-tsubo cardiomyopathy. Congestive heart failure has been reported in 3–46% of patients [3,6,7,13–19], and some patients require treatment with intraaortic balloon pumping (IABP). Left ventricular free wall rupture or septal perforation is a rare but fatal complication. Although it is difficult to predict subsequent occurrence of this complication immediately after the onset, several reports have suggested that persistent ST-segment elevation may be associated with cardiac rupture [42] (Fig. 8). It should be investigated whether early and long-term use of IABP or beta-blockers is appropriate for the prevention of cardiac rupture in patients with persistent ST-segment elevation. Hypotension occurs frequently, and it is important to identify its cause to determine appropriate management. Acute pump failure may require intravenous pressor support or mechanical support with IABP. However, in some cases, intravenous inotropic agents or IABP cause left ventricular outflow tract obstruction through the inotropic action and the reduction of afterload, respectively [43]. Bedside echocardiography can rule out this situation during these supports. Hypotension may also occur due to dynamic left ventricular outflow tract obstruction associated with the basal hypercontractility and systolic anterior movement of the mitral valve anterior leaflet. In this situation, intravenous inotropic agents would be contraindicated. In the absence of heart failure, intravenous fluids and beta-blockers may help by reducing the basal hypercontractility and increase cardiac filling, thereby reducing the obstruction [44]. Phenylephrine may be also effective by increasing the afterload and left ventricular cavity size in patients who are intolerant of intravenous fluids and beta-blockers. Left ventricular apical thrombosis may occur during the early stage due to transient apical aneurysm formation [45] (Fig. 9). In our experience, it occurred in 5.3% of patients. There are 2 types of apical thrombus; mural thrombus and protruding thrombus. Once apical thrombosis develops, an embolic event is likely to occur because the early improvement in left ventricular apical contraction may promote the discharge of apical thrombus. From this point of view, appropriate anticoagulant therapy should be performed to prevent left ventricular apical thrombosis until left ventricular apical wall motion abnormalities

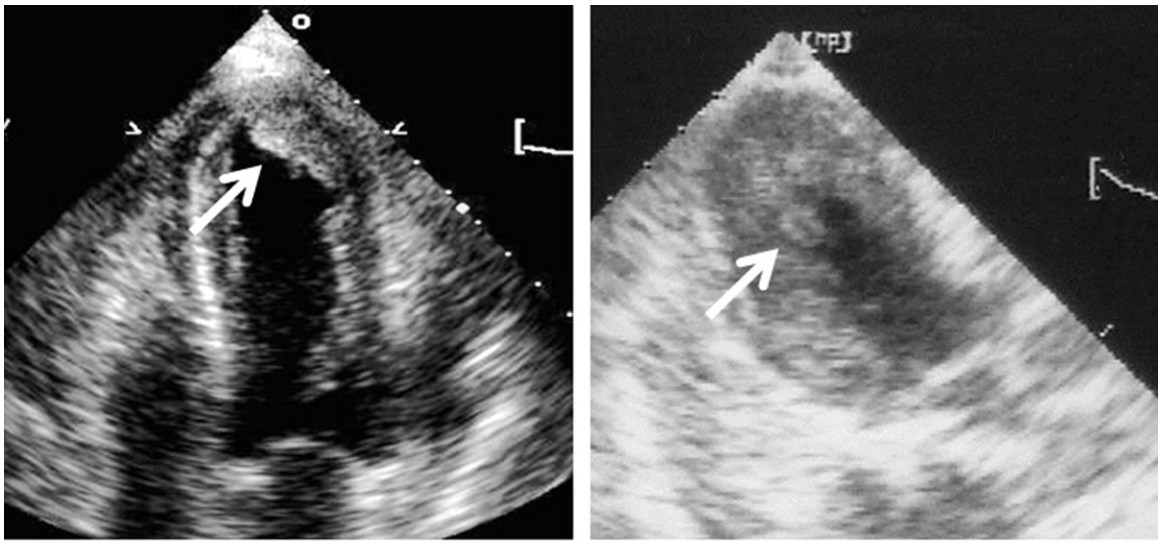

Fig. 9. Tako-tsubo cardiomyopathy complicated by left ventricular apical thrombosis. There are 2 types of apical thrombus: mural thrombus (left panel, arrow) and protruding thrombus (right panel, arrow).
Adapted from Ref. [45], with permission.

improve. Life-threatening, ventricular arrhythmias have been reported. As mentioned above, QT interval changes dynamically during the early stage. Other factors such as hypokalemia, bradycardia, or antiarrhythmic drugs may further increase the QT interval, and lead to Torsade de Pointes. We experienced 2 cases of Torsade de Pointes associated with bradycardia [46] (Fig. 10). Temporary ventricular pacing at a high rate decreased the QT interval and prevented the recurrence of Torsade de Pointes. In this situation, it is also important to correct other factors causing QT interval prolongation. Left ventricular wall motion abnormalities are usually resolved during a period of days to weeks. However, some patients have persistent left ventricular wall motion abnormalities although the precise reason remains unclear [22]. In this situation, beta-blockers, angiotensin-converting enzyme inhibitors, or angiotensin II type 1 receptor blockers are empirically recommended.

Pathophysiology

Several possible mechanisms have been proposed to explain tako-tsubo cardiomyopathy, but its pathophysiology is not well understood. Early Japanese reports including ours have suggested that tako-tsubo cardiomyopathy might result from prolonged ischemia due to multivessel epicardial coronary artery spasm [1–4]. ST-segment elevation is commonly found during the early stage even when coronary angiography shows no coronary spasm. Also, spontaneous spasm is infrequent. Because of these clinical results, multivessel coronary artery spasm is not strongly supported as a cause of tako-tsubo cardiomyopathy. We and some other groups have suggested coronary microvascular dysfunction as a cause of tako-tsubo cardiomyopathy [3,13,17,36,47,48]. We evaluated coronary angiograms in 28 patients with tako-tsubo cardiomyopathy, and found that TIMI frame count was significantly higher in all coronary arteries of patients with tako-tsubo cardiomyopathy [36]. Researchers at Mayo Clinic also found abnormal TIMI myocardial perfusion grade in 69% of patients with tako-tsubo cardiomyopathy [47]. Consistent results are reported on Doppler guidewire recording. Kume et al. reported decreased coronary flow velocity reserve as well as short diastolic deceleration in all coronary arteries of 8 patients with tako-tsubo cardiomyopathy [48]. In addition, Ito et al. reported that intracoronary injection of nicorandil acutely reduced the extent of ST-segment elevation, further suggesting coronary microvascular dysfunction during early stage [13]. On the other hand, although based on few patients, Abe et al. reported that no significant abnormality was found on Doppler guidewire or contrast echocardiography [49]. It is necessary to clarify whether coronary microvascular dysfunction is the primary cause or only a consequence of tako-tsubo cardiomyopathy. We and some groups have reported that myocardial biopsy reveals unspecific pathological findings such as adipose tissue, slight interstitial fibrosis, mildly atrophic myocardial fibers, and small numbers of mononuclear cells [3,18,49]. Myocarditis is unlikely to be a cause of tako-tsubo cardiomyopathy in the view of unspecific findings on myocardial biopsy and negative results on serum tests for viral serology. Furthermore, cardiac magnetic resonance imaging does not show regional delayed gadolinium hyperenhancement which is a feature of myocarditis [38]. Catecholamines may play a role in triggering tako-tsubo cardiomyopathy because patients often have preceding emotional or physical stress. Wittstein et al. reported high levels of catecholamines and their metabolites at the time of presentation, which remained elevated for 7–9 days [18]. On the other hand, we and some groups reported inconsistent results that circulating catecholamines were normal or not very high even immediately after the onset [3,28,50]. Lyon et al. recently have proposed that β1 (positive inotropic effects with norepinephrine) and β2 (negative inotropic effects with high levels of circulating epinephrine) adrenergic receptors are unevenly distributed through the myocardium [51]. A relative abundance of β2 receptors in the apical myocardium could explain the tendency for apical suppression with basal sparing during increased levels of circulating epinephrine. Further studies are necessary to clarify the underlying pathophysiological mechanisms of tako-tsubo cardiomyopathy.

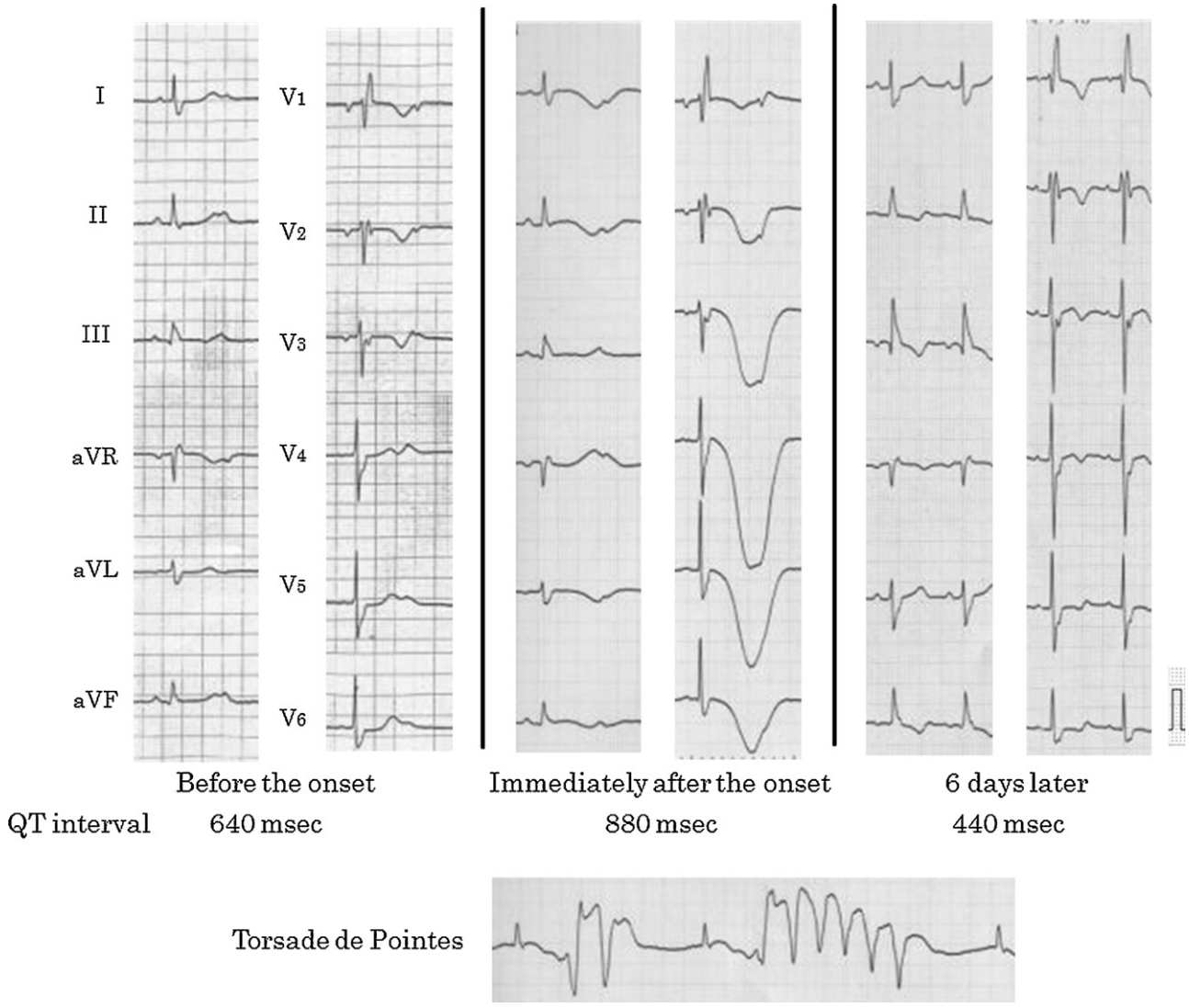

Fig. 10. Tako-tsubo cardiomyopathy complicated by Torsade de Pointes associated with bradycardia. Note the significant QT interval prolongation immediately after the onset.
Adapted from Ref. [46], with permission.

Conclusions

Tako-tsubo cardiomyopathy is an important disorder as a differential diagnosis of AMI. Precise diagnosis of tako-tsubo cardiomyopathy has important implications for clinical management especially during the early stage. Since Dr Sato first proposed the concept of tako-tsubo cardiomyopathy, more than 20 years have passed. However, its pathophysiology remains to be investigated. Further studies are necessary to clarify the underlying pathophysiological mechanisms and reach consensus in acute and long-term management.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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