Clinical Management of Takotsubo Cardiomyopathy

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Takotsubo cardiomyopathy was first reported by Sato et al at Hiroshima City Hospital in 1990 and has become increasingly recognized worldwide. In the clinical setting, takotsubo cardiomyopathy is an important disease that must be differentiated from AMI promptly for the appropriate management. Prognosis of takotsubo cardiomyopathy is generally favorable, but serious complications can occur, especially in the early stage. In this review, we summarize the current knowledge on the clinical management of takotsubo cardiomyopathy. (Circ J 2014; 78: 1559–1566)

Key Words: Cardiomyopathy; Prognosis; Reversible regional wall motion abnormality; Treatment

Takotsubo cardiomyopathy is an acute cardiac syndrome mimicking acute myocardial infarction (AMI), and is characterized by chest symptoms, electrocardiographic (ECG) changes and reversible regional wall motion abnormality (RWMA) in the apical to mid segments of the left ventricle.\(^1\)\(^2\)\(^3\)\(^4\) In contrast to AMI, takotsubo cardiomyopathy exhibits RWMA independent of acute plaque rupture or myocardial ischemia with coronary atherosclerosis during the early stage. RWMA occurs in the apical to mid segments of the left ventricle, extending beyond a single coronary territory (Figure 1), and it usually resolves spontaneously within a matter of days to a few weeks.

Takotsubo cardiomyopathy was first reported by Sato et al at Hiroshima City Hospital in 1990,\(^1\)\(^2\)\(^3\)\(^4\) since when it has become increasingly recognized worldwide. Several mechanisms, including multivessel coronary artery spasm, coronary microvascular dysfunction or catecholamine toxicity, have been proposed to explain the pathophysiology, but the precise mechanism remains unclear. In the clinical setting, takotsubo cardiomyopathy is an important disease that must be promptly differentiated from AMI for its appropriate management. Prognosis of takotsubo cardiomyopathy is generally favorable, but serious complications sometimes occur, especially in the early stage. In this review, we summarize the current knowledge on the clinical management of takotsubo cardiomyopathy.

Confirmation of Diagnosis

Patient’s Characteristics

The initial step in the management of takotsubo cardiomyopathy is the confirmation of diagnosis. Takotsubo cardiomyopathy occurs predominantly in postmenopausal elderly women.\(^3\)\(^5\) Major symptoms are chest pain and dyspnea with ECG changes. The initial presentation is very similar to AMI, but the differential diagnosis is clinically important for appropriate management. 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 V\(_1\), V\(_2\), V\(_3\) more than the sum of ST-segment elevation in leads V\(_4\)–V\(_6\) identified takotsubo cardiomyopathy with a high sensitivity and specificity.\(^14\) Kosuge et al recently reported that the combination of ST-segment depression in lead aV\(_R\) and no ST-segment elevation in lead V\(_1\) or the combination of positive T wave in lead aV\(_R\) and no negative T wave in lead aV\(_R\), was more useful in identifying takotsubo cardiomyopathy.\(^15\)\(^16\)

Electrocardiography

Common abnormalities on the initial ECG are ST-segment elevation, negative T wave and subsequent QT interval prolongation (Figure 2).\(^3\)\(^4\)\(^5\)\(^9\)\(^11\) There is a significant variability in frequency because these ECG changes are time-dependent.\(^12\)\(^13\) The typical time course of the ECG is as follows.\(^3\)\(^5\) ST-segment elevation usually occurs shortly after onset. Negative T wave deepens progressively to its first negative peak, which occurs at approximately 3 days. The negative T wave becomes shallow for several days and then deepens, the second negative peak occurring at approximately 2 weeks. QT interval becomes prolonged progressively as the negative T wave deepens. These ECG changes are found in takotsubo cardiomyopathy as well as AMI, and the differential diagnosis is clinically important for appropriate management. 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 V\(_4\)–V\(_6\) identified takotsubo cardiomyopathy with a high sensitivity and specificity. Kosuge et al recently reported that the combination of ST-segment depression in lead aV\(_R\) and no ST-segment elevation in lead V\(_1\) or the combination of positive T wave in lead aV\(_R\) and no negative T wave in lead aV\(_R\), was more useful in identifying takotsubo cardiomyopathy.\(^14\)

Echocardiography

Echocardiography plays a central role in the diagnosis of takotsubo cardiomyopathy. Typically, RWMA is found in the apical to mid segments of the left ventricle, extending beyond a single coronary territory. Relative compensatory hypercontractility is often found in the basal segment. Other patterns

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Figure 1. Left ventriculograms in typical takotsubo cardiomyopathy (Left) and the apical-sparing variant (Right).

Figure 2. Electrocardiograms in typical takotsubo cardiomyopathy (Left) and the apical-sparing variant (Right). In typical takotsubo cardiomyopathy, ST-segment elevation is found in leads I, II, aVL, aVF and V2-6. In the apical-sparing variant, ST-segment elevation is found only in leads V2 and V3. (Adapted with permission from Kurisu S, et al.)
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have been reported, such as RWMA in the mid segment with apical sparing (apical-sparing variant) (Figure 1) or right ventricular involvement. The apical-sparing variant shows limited ECG changes despite RWMA (Figure 2), and echocardiography plays an important role in the diagnosis of this variant. Echocardiography is also useful in detecting acute complications such as cardiogenic shock because of left ventricular outflow tract (LVOT) obstruction, apical thrombosis or cardiac rupture.

Coronary Angiography
In patients with suspected takotsubo cardiomyopathy, coronary angiography is useful in confirming the diagnosis. Most patients have angiographically normal coronary arteries or mild atherosclerosis. It is an important concept of takotsubo cardiomyopathy that the RWMA is not related to acute plaque rupture or myocardial ischemia with coronary atherosclerosis. Because most patients have several coronary risk factors, including advanced age, it is natural that obstructive coronary artery disease is found incidentally; in our experience, in 10% of Japanese patients with takotsubo cardiomyopathy. When obstructive coronary artery disease exists in the wrapped left anterior descending artery, it should be carefully assessed whether it is associated with RWMA in the apical segment.

Biomarkers and Laboratory Evaluation
Most patients have mildly elevated biomarkers of myocardial injury such as creatine kinase, creatine kinase-MB or troponin. Some patients even have normal levels of these biomarkers despite RWMA. Brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) are established biomarkers of heart failure, and serve as an ancillary marker for the initial diagnosis as well as follow-up. Nguyen et al revealed that BNP and NT-proBNP were substantially elevated and significantly increased during the first 24 h after onset of takotsubo cardiomyopathy, with slow and incomplete resolution during the 3 months thereafter. They showed that the peak NT-proBNP level correlated with the severity of RWMA or systolic dysfunction assessed by echocardiography.

Cardiac Imaging
Cardiac computed tomography is suitable for the differential diagnosis of takotsubo cardiomyopathy and AMI because this modality can noninvasively detect coronary atherosclerosis as well as RWMA. Magnetic resonance imaging is useful especially in assessing left ventricular function and detecting apical thrombus or right ventricular involvement. Furthermore, this modality provides information about the myocardium showing RWMA. The T2-weighted sequence usually reveals high signal intensity suggesting myocardial edema. Delayed enhancement with gadolinium, which suggests irreversible myocardial injury in AMI or myocarditis, is almost never detected in takotsubo cardiomyopathy. Single-photon emission com-

Figure 3. Echocardiographic images in cases of left ventricular apical thrombosis. There are 2 types of apical thrombus: mural thrombus (Upper, arrow) and protruding (Lower, arrow). (Adapted with permission from Kurisu S, et al.)
nary spasm is not suspected on initial presentation, because excess catecholamines may be involved in the pathophysiology. It is necessary to take care of worsening heart failure or coronary spasm after initiation of therapy. Beta-blockers may be also useful in preventing acute complications such as cardiogenic shock because of LVOT obstruction, ventricular arrhythmias or ventricular rupture.

Renin-Angiotensin-Aldosterone System Blockers
Typically, RWMA resolves spontaneously within a matter of days to a few weeks. Angiotensin-converting enzyme inhibitors or angiotensin II type 1 receptor blockers would be reasonable during the period when RWMA is present.

Therapeutic Strategies

General Principles of Therapy
Because the initial presentation mimics AMI, initial management should be directed toward the treatment of myocardial ischemia with oxygen inhalation, intravenous heparin, aspirin and β-blockers. After confirmation of takotsubo cardiomyopathy, aspirin can be discontinued if there is no incidental coronary artery disease. Thrombolytic agents should not be administered because they have no benefit in takotsubo cardiomyopathy, and can give rise to bleeding complications.

Beta-Blockers
The efficacy of β-blockers has not been fully tested. However, administration of β-blockers would be reasonable when coronary spasm is not suspected on initial presentation, because excess catecholamines may be involved in the pathophysiology. It is necessary to take care of worsening heart failure or coronary spasm after initiation of therapy. Beta-blockers may be also useful in preventing acute complications such as cardiogenic shock because of LVOT obstruction, ventricular arrhythmias or ventricular rupture.

Computed tomography also provides information on the myocardium showing RWMA. Reduced uptake of technetium-99m or thallium-201, indicating impaired myocardial perfusion, is found during the early stage. Reduced uptake of iodine-123-β-methyl-p-iodophenyl pentadecanoic acid or iodine-123-meta-iodobenzylguanidine is also found during the early stage. These markers indicate abnormal fatty acid metabolism and sympathetic denervation, respectively, which can be detected during follow-up even when the RWMA has resolved.

**Figure 4.** Electrocardiograms in a case of torsade de pointes. Bradycardia augments QT interval prolongation, resulting in torsade de pointes. (Adapted with permission from Kurisu S, et al.)

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**Anticoagulation Therapy**
Even after confirmation of takotsubo cardiomyopathy, intravenous heparin should be continued, if tolerated, to prevent left ventricular apical thrombosis. This therapy should be continued with warfarin until resolution of the RWMA in the apical segment. When resolution of RWMA has been confirmed with echocardiography, warfarin can be discontinued.
Management of Acute Complications

Congestive Heart Failure
Congestive heart failure is the most common complication, occurring in approximately 20% of patients. It occurs more frequently in patients with right ventricular involvement. Standard therapies for heart failure such as diuretics or nitroglycerin are effective in most cases. In some cases, heart failure may require aggressive pharmacological therapy with inotropic agents and mechanical circulatory support with intraaortic balloon pumping (IABP). When patients have severe congestive heart failure or significant hypotension, it is important to assess whether LVOT obstruction or mitral regurgitation is associated with their condition. Echocardiography plays a central role in the diagnosis of LVOT obstruction or mitral regurgitation.

Cardiogenic Shock
Hypotension occurs frequently, so it is important to identify its cause by echocardiography or cardiac catheterization in order to determine the appropriate management. Cardiogenic shock can result from LVOT obstruction associated with basal hypercontractility. LVOT obstruction may be associated with systolic anterior movement of the mitral valve anterior leaflet and mitral regurgitation. When LVOT obstruction is identified, nitroglycerin or inotropic agents should be immediately discontinued to avoid further obstruction. In the absence of severe heart failure, intravenous fluids or β-blockers would be reasonable because they suppress the basal hypercontractility and increase cardiac filling, thereby reducing the obstruction. Verapamil or diltiazem may provide hemodynamically favorable effects similar to β-blockers. When coronary spasm is suspected, calcium-channel blockers would be more appropriate than β-blockers. Phenylephrine may be also effective by increasing the afterload and left ventricular cavity size in patients who are intolerant of intravenous fluids and β-blockers.

Cardiogenic shock because of acute pump failure is treated with intravenous fluids, inotropic agents or IABP. However, in some cases, inotropic agents and IABP cause LVOT obstruction through basal hypercontractility and reduced afterload, respectively. These adverse effects may cause further hemodynamic deterioration. Echocardiography is also useful in detecting the adverse effects of these treatments.

Apical Thrombosis
Left ventricular apical thrombosis may occur because of RWMA in the apical segment. Low blood flow within the apical segment is the presumed cause of apical thrombosis. In our practice, it was found in 5.3% of Japanese patients during the early stage. There are 2 types of apical thrombus: mural and protruding (Figure 3). The clinical importance is that the apical thrombosis is a potential source of emboli. Cerebral ischemic attack or renal infarction has been identified in previous cases. If apical thrombosis occurs, early resolution of RWMA, which is the nature of takotsubo cardiomyopathy, may accelerate its discharge. It is important to prevent apical thrombosis.

Figure 5. Electrocardiograms in a case of cardiac rupture. Note that ST-segment elevation persists even 35 h after admission. (Adapted with permission from Kurisu S, et al.)
in advance, so prophylactic anticoagulation therapy should be considered to prevent apical thrombosis and further embolic events until the resolution of RWMA in the apical segment.

Arrhythmias
Madias et al reported that life-threatening ventricular arrhythmias such as torsade de points (TdP) and ventricular fibrillation occurred in 8.6% of patients with takotsubo cardiomyopathy. They pointed out that patients with corrected QT interval (QTc) interval >500ms had an increased risk of life-threatening ventricular arrhythmias. Migliore et al also recently reported that TdP requiring external defibrillation occurred in 4.9% of patients with giant negative T waves and QTc interval >500ms during the subacute stage. The QTc interval changes day to day over several weeks, and TdP is likely to occur in the setting of QTc interval prolongation. Bradycardia, hypokalemia, hypomagnesemia or use of antiarrhythmic drugs may augment QTc interval prolongation. We reported 2 cases of both takotsubo cardiomyopathy and bradycardia complicated by TdP (Figure 4), and demonstrated that temporary ventricular pacing at a high rate was useful in decreasing the QT interval and preventing its recurrence. Purvis et al reported the effect of intravenous magnesium in a case of both takotsubo cardiomyopathy and hypomagnesemia complicated by TdP. It is necessary to correct the risk factors of QTc interval prolongation to prevent or treat TdP. By the way, Migliore et al reported that ECG abnormalities and RWMA disappeared 1 month later in patients receiving an implantable cardioverter-defibrillator, and these patients did not require device interventions during follow-up. Those results suggest that arrhythmia events occur during reversible QTc interval prolongation in the hospital course.

Presumed new onset of atrioventricular (AV) block has been shown in previous cases. AV block resolved in some patients, but persisted in others even after resolution of the RWMA. It remains unclear whether the AV block associated with takotsubo cardiomyopathy requires pacemaker implantation or when it should be considered. However, when AV block results in hemodynamic instability or marked QTc interval prolongation, temporary ventricular pacing should be considered at least.

Arrhythmias in takotsubo cardiomyopathy should be managed on a case-by-case basis. The reversible nature of this disease seems not to justify systematic device implantation in patients who experienced life-threatening ventricular arrhythmias or AV block during hospitalization.

Ventricular Rupture
Left ventricular free wall rupture or septal perforation is a rare but life-threatening complication (Figure 5). It is clinically difficult to predict its subsequent occurrence on admission. However, Kumar et al showed that patients with cardiac rupture were older and had higher double product, higher left ventricular peak systolic blood pressure, higher frequency of persistent ST-segment elevation and lower frequency of use of ß-blockers. These results suggest that cardiac rupture is associated with higher left ventricular intramural pressure and wall stress. The study also reported that 10 (83%) of the 12 patients with cardiac rupture died, and 90% of deaths occurred within approximately 8 days. The role of ß-blockers to prevent cardiac rupture is well-established in AMI, but remains unclear in takotsubo cardiomyopathy. However, ß-blockers would be reasonable, at least in patients with high double product or persistent ST-segment elevation.

Course and Prognosis
In most cases, RWMA resolves spontaneously within a matter of days to a few weeks. However, we previously reported 2 cases of takotsubo cardiomyopathy in which RWMA persisted for more than 3 months. Lee et al and Shim et al each recently reported similar cases of persistent takotsubo cardiomyopathy complicated by apical thrombosis. Thus, in some cases, RWMA persists despite the usual hospital course during early stage. The precise reason remains unclear. In these cases, the patients require long-term management of heart failure or apical thrombosis.

The in-hospital death rate ranges from 0% to 8%. Prognosis is generally favorable, but a small subset has potentially life-threatening complications. Several studies have recently shown that the ECG or echocardiographic findings at initial presentation may be useful for predicting short-term prognosis beyond diagnosis. Shimizu et al showed that the J wave, which appeared transiently only during the very early stage, was an indicator of cardiac death and/or ventricular tachyarrhythmia. Citro et al reported that left ventricular ejection fraction, E/e' ratio and reversible moderate to severe mitral regurgitation were independent correlates of major adverse cardiac events. Takotsubo cardiomyopathy can occur in critically ill patients, and their outcome appears to be dependent on the underlying condition rather than the takotsubo cardiomyopathy itself.

Recurrence rate ranges from 0% to 15%. Elesber et al reported recurrence in 10% of patients over a mean follow-up of 4.4±4.6 years, and that recurrence was highest within the first 4 years, subsequently decreasing over the remainder of their follow-up. Several case reports have shown that takotsubo cardiomyopathy can present with typical RWMA in the apical segment at initial presentation and atypical RWMA with apical sparing during a recurrence. We have previously reported that takotsubo cardiomyopathy can occur despite treatment with calcium-channel blockers, nitrates, ß-blockers, statins or aspirin. Elesber et al also showed that there was no difference in the use of angiotensin-converting enzyme inhibitors/angiotensin II type 1 receptor blockers, ß-blockers, statins or aspirin between patients with recurrence and those without. These results suggest the limiting medical treatment for the prevention of takotsubo cardiomyopathy. There appears to be no consensus regarding the management of long-term follow-up. It is necessary to clarify the pathophysiology of takotsubo cardiomyopathy for establishing its optimal management.

Conclusions
Takotsubo cardiomyopathy is an important disease that has to be differentiated from AMI promptly for appropriate management. Its prognosis is generally favorable, but monitoring the clinical course is essential to prevent or treat acute complications. It is necessary to clarify the pathophysiology of takotsubo cardiomyopathy for establishing its optimal management.

Disclosures
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References


