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Review

Update of takotsubo syndrome in the era of COVID-19

Hiroyuki Okura (MD, FJCC)*

Department of Cardiology, Gifu University Graduate School of Medicine, 1-1 Yanagido, Gifu, 501-1194, Japan

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SUMMARY

Takotsubo cardiomyopathy or takotsubo syndrome (TTS) has become a well-known disease not only in Japan but also in the rest of the world. Early reports suggested that TTS is a self-limiting disease with better prognosis than acute coronary syndrome. However, recent data showed that TTS is not a benign disease as compared with acute coronary syndrome. In addition to the apical ballooning, several other types of wall motion abnormalities have been classified as variants of TTS. In particular, right ventricular involvement, or biventricular TTS, is not uncommon and is associated with poor in-hospital as well as long-term outcomes. With respect to the pathophysiology, modulation (desensitization) of the beta-adrenergic receptor is suspected as a possible mechanism for transiently depressed myocardial contraction. Although specific treatments to improve prognosis of TTS are still uncertain, observational data suggest favorable impact of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Finally, in the era of COVID-19, we should pay attention to a variety of cardiovascular conditions related to COVID-19. TTS is one of these conditions that can be triggered by both emotional and physical impact of the COVID-19 pandemic.

Contents

Introduction

Since the initial reports from Japan [1–4], takotsubo cardiomyopathy or takotsubo syndrome (TTS) has become globally recognized as a unique syndrome mimicking acute coronary syndrome triggered by emotional or physical stress [5]. Initially, emotional stress was considered as essential for TTS and thus TTS was also named as stress-induced cardiomyopathy. However, emotional stress was documented in only 20-39% and physical stress in 35-55% of cases [6]. Interestingly, not only negative emotional stress but also positive emotional stress could be a trigger of TTS, and it has been called “happy heart syndrome” [7]. Natural disasters may cause a variety of cardiovascular diseases, such as acute myocardial infarction [8,9], stroke [10], deep vein thrombosis [10,11], and TTS [12,13]. Currently, the pandemic of COVID-19 affects the health status of people all over the world. SARS-CoV-2 is a newly found corona virus that sometimes causes catastrophic respiratory failure requiring respirator and/or extracorporeal membrane oxygenation. In this review, a current update of TTS in the era of COVID-19 pandemic is summarized.

* Corresponding author. Phone: +81-59-230-6520; Fax: +81-58-230-6524.
E-mail address: hokura@fides.dti.ne.jp

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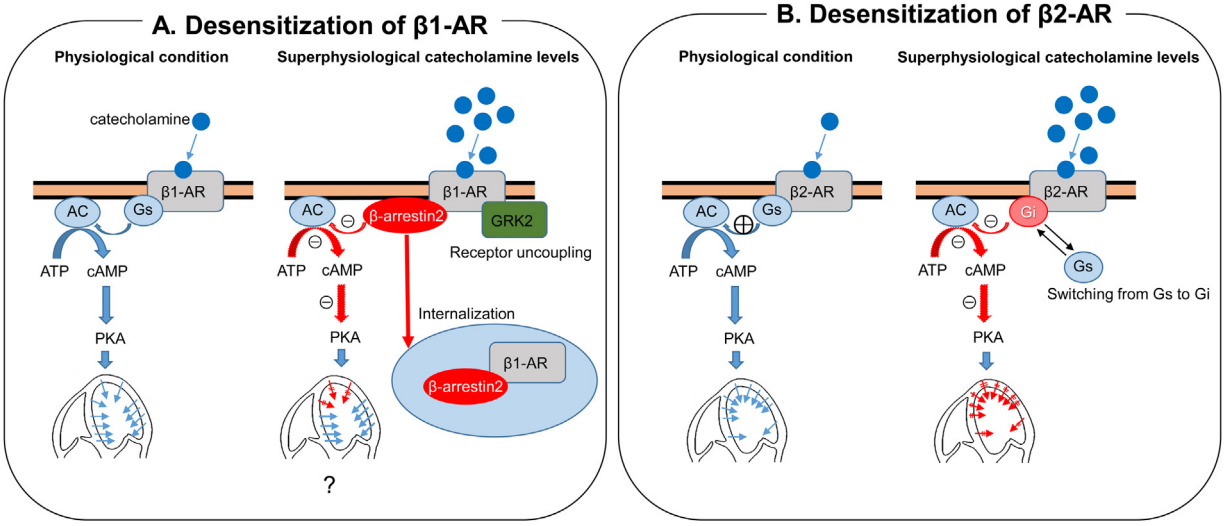

Fig. 1. Proposed mechanisms of wall motion abnormalities in patients with takotsubo syndrome. (A) With superphysiological catecholamine levels, β-arrestin2 internalization the β1-AR and GRK2 induces β1-AR uncoupling, resulting in desensitization and suppression of myocardial contraction. Adapted from Nakano et al. [19]. (B With superphysiological catecholamine levels, stimulation of β2-AR suppress myocardia contraction by switching Gs protein to Gi protein. Adapted from Paur et al. [17].

Pathophysiology and mechanisms of TTS

Although catecholamine has been suspected to play some role during the development of TTS, exact mechanisms of TTS are still uncertain. In TTS patients, plasma catecholamine (epinephrine, norepinephrine, and dopamine) levels at presentation were markedly higher than among those with Killip class III myocardial infarction [14]. We further compared catecholamine levels at the aortic root and coronary sinus and demonstrated local release of catecholamine levels (norepinephrine) in TTS [15]. Akashi et al. reported increased iodine-123-meta-iodobenzylguanidine uptake and increased washout ratio in the acute phase of TTS, suggesting the presence of cardiac sympathetic hyperactivity [16]. Paur et al. reported interesting results of an in vivo rat model of TTS. They suggested that high-dose epinephrine can induce direct cardiomyocyte cardiodepression and cardioprotection in a β2-adrenergic receptor (AR)–Gi-dependent manner [17]. At higher concentrations, epinephrine stimulates a negative inotropic effect on myocardial contraction by switching β2-AR coupling from Gs protein to Gi protein [18]. Stimulation of the β2-AR-Gi protein pathway then produces negative inotropic action resulting in akinesis of the involved segments. Location and the extent of wall motion abnormalities in TTS may be explained by the distribution of the β2-AR [18]. More recently, we demonstrated in vivo evidence of β-AR alteration [19]. Left ventricular biopsy samples from patients with TTS demonstrated more abundantly expressed G protein coupled receptor kinase 2 (GRK2) and β-arrestin2, both of which are known to desensitize β-AR, than in samples from dilated cardiomyopathy. Desensitization of β1-AR causes decreased left ventricular contraction of the involved segments. In cases with apical TTS, apical segments may be more involved, although exact mechanisms of the segment specific changes in desensitization of the β1-AR are unclear. Desensitization of β1-AR together with switching of the coupling G protein from Gs to Gi in β2-AR could explain apical involvement because of its apical dominant distribution [17–19] (Fig. 1).

New classification and diagnostic criteria of TTS

Originally, only those who presented left ventricular apical ballooning or takotsubo-like wall motion were diagnosed as having

Table 1
InterTAK diagnostic criteria.

	International Takotsubo Diagnostic Criteria (InterTAK Diagnostic Criteria)
1.	Patients show transient left ventricular dysfunction (hypokinesia, akinesia, or dyskinesia) presenting as apical ballooning or midventricular, basal, or focal wall motion abnormalities. Right ventricular involvement can be present. Besides these regional wall motion patterns, transitions between all types can exist. The regional wall motion abnormality usually extends beyond a single epicardial vascular distribution; however, rare cases can exist where the regional wall motion abnormality is present in the subtended myocardial territory of a single coronary artery (focal takotsubo syndrome).
2.	An emotional, physical, or combined trigger can precede the takotsubo syndrome event, but this is not obligatory.
3.	Neurologic disorders (e.g. subarachnoid hemorrhage, stroke/transient ischemic attack, or seizures) as well as pheochromocytoma may serve as triggers for takotsubo syndrome.
4.	New electrocardiographic (ECG) abnormalities are present (ST-segment elevation, ST-segment depression, T-wave inversion, and QTc prolongation); however, rare cases exist without any ECG changes.
5.	Levels of cardiac biomarkers (troponin and creatine kinase) are moderately elevated in most cases; significant elevation of brain natriuretic peptide is common.
6.	Significant coronary artery disease is not a contradiction in takotsubo syndrome.
7.	Patients have no evidence of infectious myocarditis.
8.	Postmenopausal women are predominantly affected.

Adapted from Ghadri et al. [22].

Table 2
InterTAK Diagnostic Score.

	Score	OR (95%CI)	*p*
Female	25	68 (29.0–163.7)	<0.001
Emotional trigger	24	65 (20.3–205.8)	<0.001
Physical trigger	13	8.7 (4.6–17.3)	<0.001
Absence of ST depression	12	7.2 (3.1–16.8)	<0.001
Psychiatric disorder	11	7.0 (3.1–15.5)	<0.001
Neurogenic disorder	9	4.9 (2.2–11.3)	<0.001
QTc prolongation	6	2.8 (1.3–5.7)	0.006

Adapted from Ghadri et al. [25].

takotsubo cardiomyopathy or TTS, because only left ventriculography was used to assess wall motion abnormality [5]. As multimodality images have become available [20], we now recognize that apical ballooning was only a part of TTS. A recently published consensus document of multimodality images on TTS well described the role of multimodality images in TTS [20]. There is no doubt that echocardiography plays a pivotal role in the assessment of TTS [6]. Mayo criteria [21] and InterTAK criteria (Table 1) [22,23] are well recognized diagnostic criteria. Importantly, InterTAK criteria describe that the presence of pheochromocytoma [1] and significant coronary artery disease (CAD) [24] are not contradictory to the diagnosis of TTS. Because clinical presentation of TTS mimics acute coronary syndrome, the differential diagnosis between the two syndromes is challenging. To differentiate TTS and acute coronary syndrome, the InterTAK Diagnostic Score has been proposed. The InterTAK Diagnostic Score is formed using seven variables, and each was assigned a score value: female sex 25, emotional trigger 24, physical trigger 13, absence of ST-segment depression (except in lead aVR) 12, psychiatric disorders 11, neurologic disorders 9, and QTc prolongation 6 points (Table 2). When patients with a score of $\geq$50 were diagnosed as having TTS, nearly 95% of TTS patients were correctly diagnosed [25].

Detection of wall motion abnormalities by left ventriculography and echocardiography

Although left ventriculography was originally used to detect its unique morphology mimicking "takotsubo", echocardiography is currently an essential imaging modality to detect segmental as well as global wall motion abnormalities in patients with TTS. In addition to the apical ballooning (Fig. 2), there are several subtypes of TTS based on the location and extension of asynergy (Fig. 3). Prevalence of apical, mid-ventricular (Fig. 4), basal, and focal types are 62-88%, 10-18.5%, 0-5.8%, and 0-6.1%, respectively [26–31]. Importantly, right ventricular wall motion could be involved with and without left ventricular wall motion abnormalities [6,26,27,32]. Because earlier studies used left ventriculography to detect and diagnose TTS, right ventricular involvement had not been reported until 2006, when two studies from the USA and EU reported right ventricular involvement in TTS [33,34]. In addition, a study using cardiac magnetic resonance imaging revealed the presence of right ventricular involvement in 81 of 239 (34%) TTS patients [35]. Presence of right ventricular involvement, or biventricular TTS, are associated with worse in-hospital as well as long-term clinical outcomes [26,27,36] (Fig. 5). Right ventricle

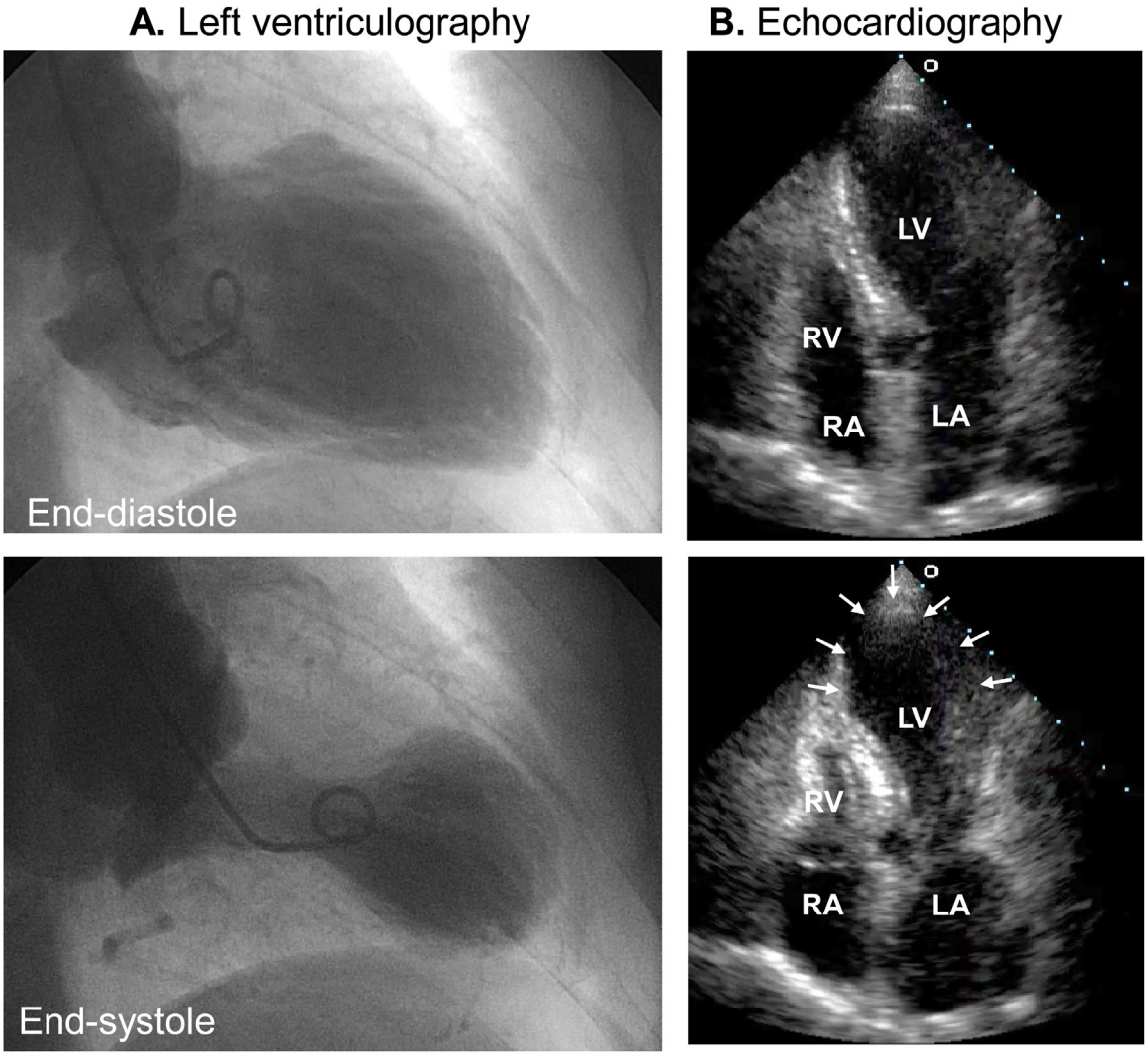

Fig. 2. Apical takotsubo syndrome. (A) Left ventriculography demonstrates typical apical ballooning, or "takotsubo"-like appearance. (B) Echocardiography demonstrates akinesis of the apical segment (arrows).
LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

Classification (Type of TTS)	Kagiyama (n=113)	Citro (n=227)	InterTAK (n=1,750)	GEIST (n=1,071)	RETAKO (n=293)
Apical	64.6 %	77.1%	81.7 %	88 %	62 %
Mid- Ventricular	18.6 %	18.1 %	14.6 %	10 %	12 %
Basal	0 %	4.8 %	2.2 %	2 %	3.7 %
Focal	0%	NA	1.5 %	NA	6.1 %
Biventricular	16.8 %	24.5 %	NA	NA	NA

Fig. 3. Classification of takotsubo syndrome based on the location of wall motion abnormalities.
Adapted from Kagiyama et al. [26], Citro et al. [28], Templin et al. [29], Uribarri et al. [30], and Arcari et al. [31].

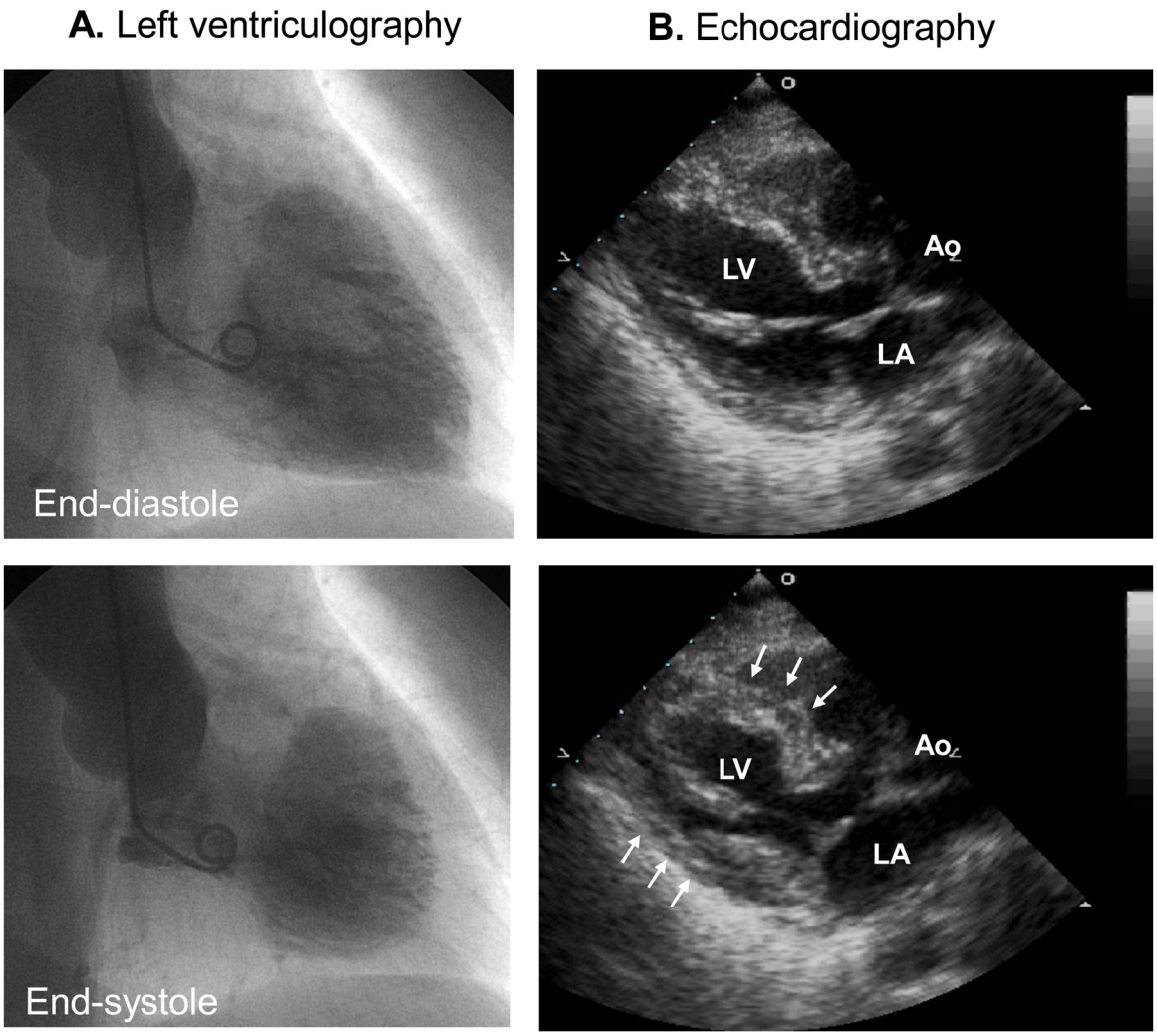

Fig. 4. Mid-ventricular takotsubo syndrome. (A, B) Both left ventriculography and echocardiography demonstrated akinesis (arrows) of the mid-ventricular segment.
Ao, aorta; LA, left atrium; LV, left ventricle.

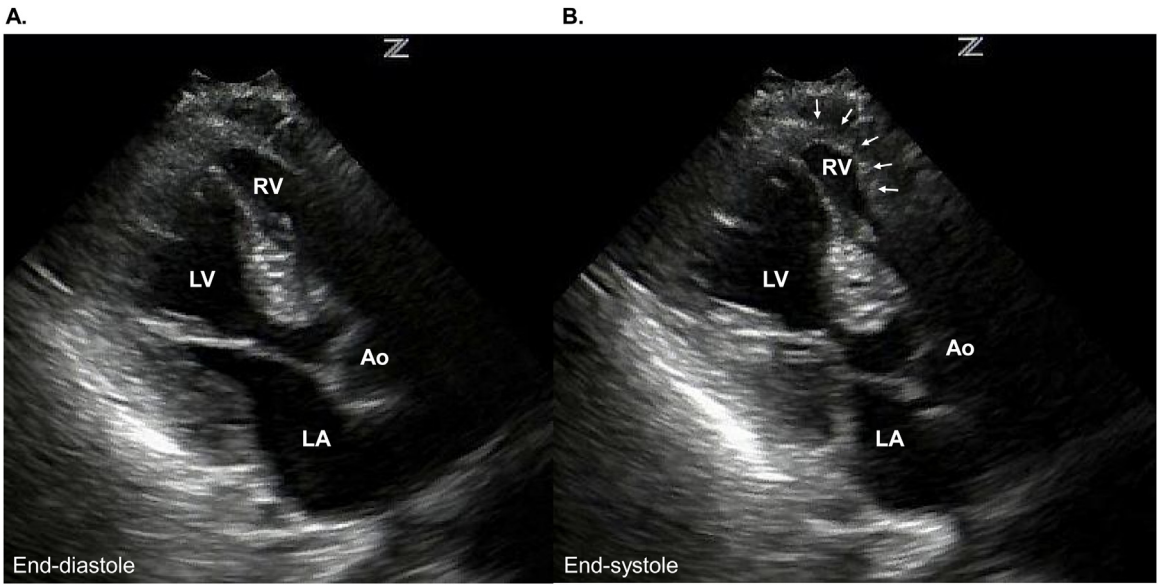

Fig. 5. Biventricular takotsubo syndrome. Apical long-axis view of the echocardiography [end-diastole (A) and end-systole (B)] demonstrates akinesis of LV and RV (arrows). Ao, aorta; LA, left atrium; LV, left ventricle; RV, right ventricle.

may be involved without left ventricular wall motion abnormalities (isolated right ventricular TTS) [37–41].

Unfavorable echocardiographic findings related to TTS

Echocardiography is useful to detect unfavorable findings related to TTS [6]. First, left ventricular outflow tract obstruction (LVOTO) may develop in TTS patients with apical ballooning and a hyperkinetic basal wall motion (Fig. 6). LVOTO is usually complicated in patients with hypertrophic obstructive cardiomyopathy or elderly patients with sigmoid septum [42].

In TTS, preexisting septal bulge and hyperkinetic septal motion are possible causes of LVOTO. Prevalence of LVOTO among TTS patients ranges from 9.7% to 33% [27,43–46]. LVOTO is an important cause of hypotension and heart failure during acute phase of TTS because use of positive inotropic agent and/or diuretics usually exaggerates LVOTO and as a result, deteriorate hemodynamic condition. Use of a beta-blocker, hydration in addition to cessation of positive inotropic agents, diuretics, or vasodilators are reasonable treatments for LVOTO. LVOTO sometimes causes acute mitral regurgitation [47] as a result of systolic anterior motion (SAM) of the anterior mitral leaflet, further deteriorating hemodynamic conditions. Prevalence of mitral regurgitation in TTS ranges from 15%-21.5% [27,28,48]. Acute mitral regurgitation is associated with major adverse events (a composite of acute heart failure, cardiogenic shock, and in-hospital mortality) [28] and therefore careful observation and treatment are mandatory. In addition to LVOTO, tethering of the mitral leaflet due to acute left ventricular dilatation may cause transient and significant mitral regurgitation [49]. Detection of the mechanisms

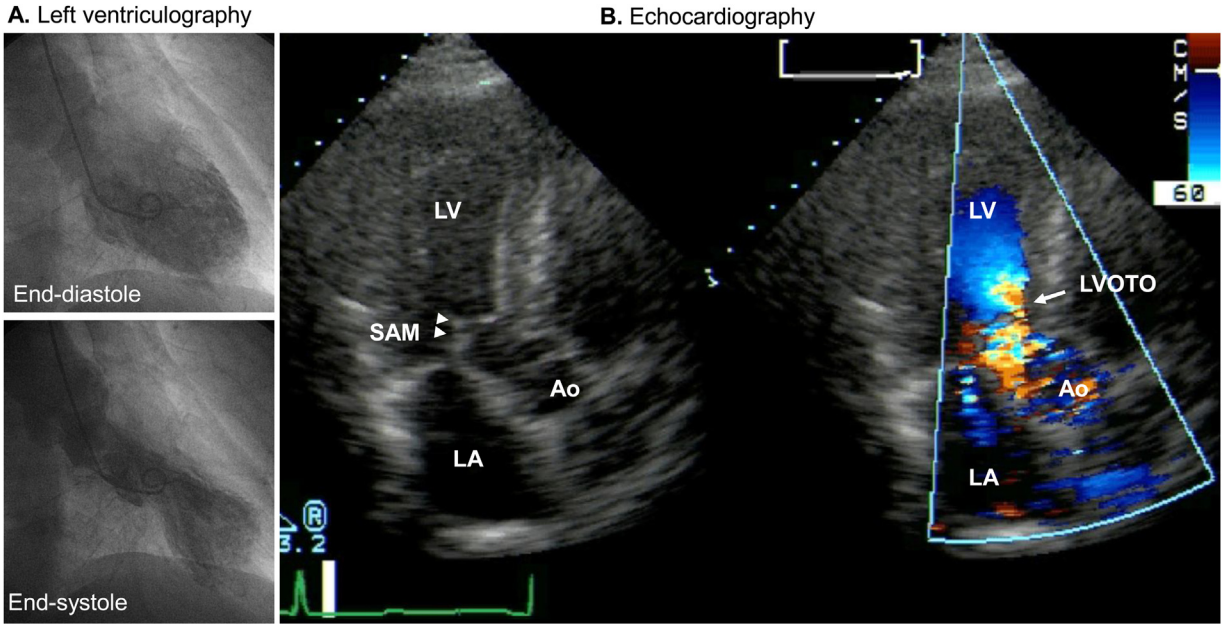

Fig. 6. Left ventricular outflow tract obstruction (LVOTO) in takotsubo syndrome. (A) Left ventriculography shows apical ballooning. (B) Echocardiography shows LVOTO (arrow) and mitral regurgitation caused by systolic anterior motion (SAM) of the anterior mitral valve (arrow heads).
Ao, aorta; LA, left atrium; LV, left ventricle.

of mitral regurgitation by echocardiography is important because of its implications for treatment. As mentioned above, diuretics, vasodilators, or positive inotropes should be avoided in patients with mitral regurgitation caused by LVOTO. On the other hand, mitral regurgitation caused by leaflet tethering may be better treated with such medications.

Left ventricular thrombus may develop during acute phase of TTS and its prevalence ranges from 2.2% to 8% [27,50–53]. According to the largest study, 12 of 541 (2.2%) TTS patients had left ventricular thrombus and 2 strokes were documented before initiation of anticoagulation [53]. Oral anticoagulation is recommended until the left ventricular thrombus has resolved and the wall motion recovered.

A very rare but critical complication is left ventricular free wall or septal rupture [54–60]. Persistent ST elevation may be a high-risk electrocardiographic finding for left ventricular rupture [57].

Co-existence of coronary artery disease and TTS

In both Mayo criteria [21] and InterTak diagnostic criteria [22] significant CAD is not an exclusion criteria of TTS. Indeed, coexistence of acute coronary syndrome has been reported in 10-29% of TTS patients [29,61,62]. Acute coronary syndrome may not only coexist but also can trigger the TTS. In our recent study including 413 patients who were admitted to a cardiac care unit (CCU), we found 5 patients with acute myocardial infarction also had TTS based on retrospective review of the echocardiographic images [24]. Fig. 7 shows echocardiographic images from a patient with acute posterior myocardial infarction. Apical ballooning was clearly detected which cannot be explained by the left circumflex coronary artery lesion. As expected, presence of CAD in patients with TTS is a sign of worse prognosis. A recent study including 1016 TTS patients demonstrated that non-obstructive CAD was present in 23.0% and obstructive CAD in 41.2% of the TTS patients [63]. Presence of CAD was associated with increased incidence of shock, ventilation, and death from any cause. Furthermore, TTS patients with obstructive CAD were at comparable risk for shock and death and nearly at twice the risk for ventilation compared to an age- and sex-matched acute coronary syndrome cohort [63]. In addition to CAD, various cardiac diseases can trigger or coexist with TTS. In our above-mentioned study, aortic stenosis, cardiac amyloidosis, and tachycardia-induced cardiomyopathy coexisted or triggered TTS in CCU [24]. Fig. 8 is from a patient who was admitted to our hospital because of recurrent episodes of acute decompensated heart failure. An echocardiography at the previous admission demonstrated diffuse left ventricular hypertrophy and mildly depressed left ventricular systolic function and impaired left ventricular diastolic function. In echocardiography at the time of recurrent episode of heart failure (Fig. 8 A,B), we noticed biventricular apical asynergy that was not detected before.

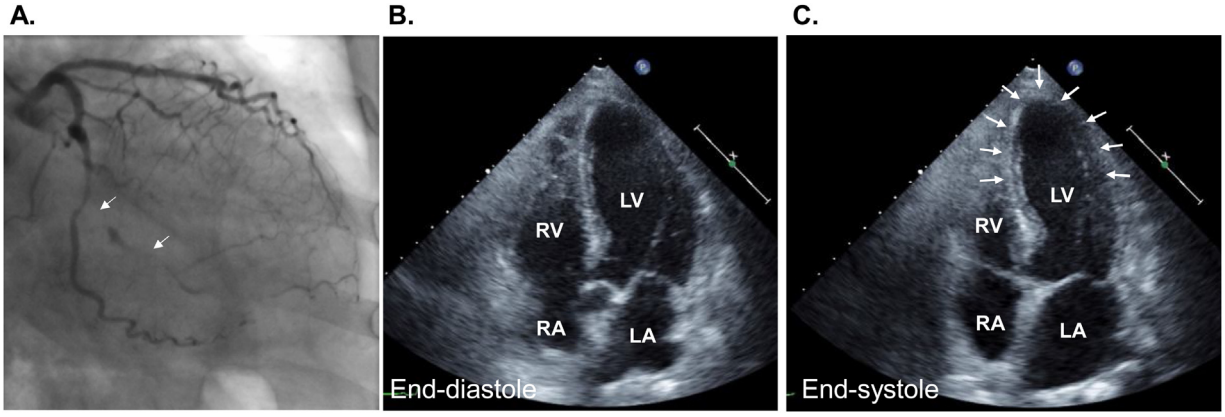

Fig. 7. A case of takotsubo syndrome complicated with posterior myocardial infarction. (A) Coronary angiogram shows occlusion of the postero-lateral branch of the left circumflex coronary artery (arrows). (B, C) Echocardiography shows akinesis of the apical segment (arrows) that cannot be explained by the coronary artery occlusion. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

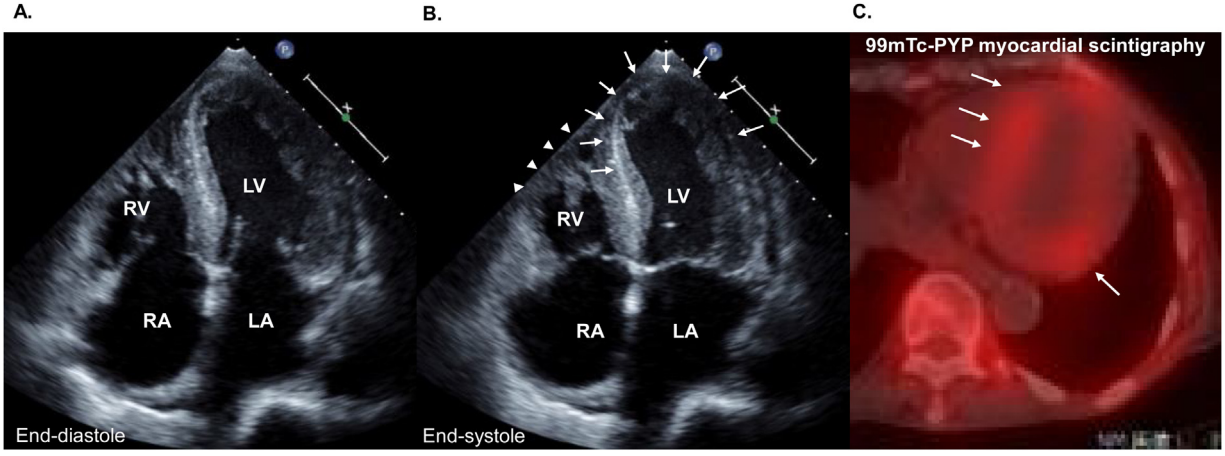

Fig. 8. A case of takotsubo syndrome complicated with cardiac amyloidosis. (A, B) Echocardiography shows diffuse left ventricular hypertrophy and hypokinesis and akinesis of the left (arrows) and right ventricular (arrow heads) apical segments.
(B) 99 m Tc-pyrophosphate (99 m Tc-PYP) myocardial scintigraphy demonstrates significant uptake (arrows), suggesting the diagnosis of transthyretin cardiac amyloidosis. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

Coronary angiography was normal and technetium pyrophosphate scintigraphy demonstrated significant uptake suggestive of transthyretin cardiac amyloidosis (Fig. 8C). She was diagnosed with TTS complicated with transthyretin cardiac amyloidosis. A recent Japanese nationwide survey including 5274 patients with TTS revealed that 3255 (61.7%) underwent coronary angiography and 2019 (38.3%) did not [64]. Although prognosis between TTS with and without coronary angiography did not differ, TTS patients complicated with CAD may be underdiagnosed.

Prognosis of TTS

As mentioned above, prognosis of TTS has been recognized as benign. However, recent studies consistently reported in-hospital mortality of 3.5-10.6% comparable to that of acute coronary syndrome [26,29,65–67]. Data from the Tokyo Coronary Care Unit Network including 107 patients with TTS demonstrated high in-hospital complications including 37 pump failure and 2 sustained ventricular tachycardia or fibrillation and 2 atrioventricular block [68]. As expected, TTS with cancer/malignancy had significantly lower survival [69,70]. Similarly, TTS triggered by physical stress had significantly lower survival than those by emotional stress or no stress [67,69]. InterTAK classification demonstrated that 5-year mortality is higher in class IIa [physical activities, medical conditions, or procedures, HR = 3.78 (95% CI: 2.21–6.44), $p < 0.0001$], class IIb [neurologic disorders, HR=5.76 (95% CI:2.96−11.2), $p < 0.0001$], and class III [no stress factor, HR=2.14 (95% CI:1.20−3.82), $p = 0.010$] as compared with class I (emotional stress) [67].

Although most cases of TTS are self-limiting, there are subsets of patients who develop recurrent episode of TTS [23,71]. Data from the Swedish Coronary Angiography and Angioplasty Register between 2009 and 2013 demonstrated that the mortality of TTS is worse than in control subjects without CAD and similar to patients with CAD [72]. Data from the InterTAK registry database demonstrated that a rate of death from any cause of 5.6% per patient-year and a rate of major adverse cardiac and cerebrovascular events of 9.9% per patient-year [29]. A recent meta-regression analysis including 4679 patients from 54 studies demonstrated that the annual rate of total mortality was 3.5% and that of recurrence was 1.0%, respectively [73].

Treatment of TTS

As of today, no randomized prospective study has been conducted to assess the prognostic impact of any specific medication on prognosis of TTS. Considering the possible role of catecholamine toxicity on TTS, it is reasonable to consider the use of beta-blockers. Isogai et al. compared 422 TTS patients who were treated with early beta-blocker therapy and 1688 propensity score matched controls and found that early beta-blocker use was not associated with lower 30-day mortality [74]. Results from the InterTAK registry demonstrated that survival was comparable between patients with and those without beta-blockers at discharge [29]. On the other hand, the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers at discharge was associated with improved survival [29]. With respect of recurrence of TTS, a meta-analysis demonstrated that angiotensin-converting enzyme inhibitors or angiotensin receptor blockers rather than beta-blockers may reduce risk of recurrence [71]. A retrospective study suggested that antiplatelet therapy especially aspirin may be beneficial [75]. However, a recent larger scale study with longer (5 years) follow-up period demonstrated no association between aspirin use in TTS patients and a reduced risk of major adverse cardiovascular and cerebrovascular events at 30-day and 5-year follow-up [76].

Table 3
Takotsubo syndrome associated with COVID-19.

	Age	Gender	Symptom	Electrocardiography	Type
Case 1	83	Female	Chest pain	ST elevation, T inversion	Apical
Case 2	67	Female	Fever, cough	RBBB, T inversion	Apical
Case 3	52	Male	Shortness of breath	ST elevation	Apical
Case 4	50	Male	Chest pain	ST elevation	Mid-ventricular

Adapted from Fried et al. [82], Meyer et al. [83],Sattar et al. [84], and Taza et al. [85].
RBBB, right bundle branch block.

COVID-19 and TTS

Currently, the pandemic of corona virus disease 19 (COVID-19) affects health status of the people all over the world. SARS-CoV-2 is a newly found corona virus that sometimes causes catastrophic respiratory failure requiring respirator and/or extracorporeal membrane oxygenation. It is reported that myocardial injury was present in 7.2% of patients with COVID-19 [77]. In particular, 22% of the COVID-19 patients admitted to intensive care unit had evidence of myocardial injury [77]. Importantly, myocardial injury is associated with worse prognosis of COVID-19 [78]. Acute myocarditis is one of the important causes of cardiac injury [79–82]. In addition, several other cardiac complications may develop during the course of COVID-19 [82]. It is not surprising that TTS can develop in patients with COVID-19 considering its stressful physical as well as psychological situation. Meyer et al. first reported a typical case (apical ballooning) of TTS complicated with COVID-19 [83]. Both emotional stress and physical stress by infection itself are considered as possible triggers of typical [83–85] as well as atypical [86] TTS in patients with COVID-19 (Table 3). Not only the COVID-19 patient, but also his or her family may develop TTS possibly as a result of stressful situations [87]. During the diagnostic work up, care should be taken to keep sonographers and doctors safe [88,89]. Furthermore, it is recommended to perform coronary computed tomography rather than coronary angiography to rule out the presence of CAD [20].

Disclosure

Nothing to disclose related to this article.

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