30

Takotsubo Cardiomyopathy

Abdul Moiz Hafiz[1], M. Fuad Jan[2], Timothy E. Paterick[2], Suhail Allaqaband[2] and A. Jamil Tajik[2]
[1]*Winthrop-University Hospital, Mineola, New York,*
[2]*Aurora Cardiovascular Services, Aurora Sinai/Aurora St. Luke's Medical Centers, University of Wisconsin School of Medicine and Public Health, Milwaukee, Wisconsin, USA*

1. Introduction

Since the first report in 1990, takotsubo cardiomyopathy (TTC) has been increasingly recognized as a novel form of nonischemic acute cardiomyopathy. It is an important differential in diagnosis of acute coronary syndrome (ACS) due to its similar presentation. However, it distinguishes itself from an ACS in the fact that regional wall motion abnormalities extend beyond a single coronary vascular bed and are reversible, and epicardial coronary occlusion is absent (1).

In TTC, left ventricular (LV) dysfunction can be remarkably depressed but recovers within a few weeks (2) in the vast majority of patients. This syndrome has been described by more than 75 individual descriptive names in the literature, emphasizing those disease features that were most impressive to individual investigators (3) (Table 1).

Increased awareness about this syndrome has led to its incorporation into the American Heart Association classification of reversible cardiomyopathies (4,5). Pathogenesis of this syndrome is still not well understood, although physical and emotional stressors and mediation by pathologic sympathetic myocardial stunning are believed to play key roles. However, in an important minority of patients, a detailed personal history does not elicit an antecedent event (3).

Apical ballooning
Apical ballooning syndrome
Acute left ventricular apical ballooning syndrome
Left ventricular apical ballooning syndrome
Transient left ventricular apical ballooning syndrome
Primary apical ballooning
Transient apical ballooning
Transient apical ballooning syndrome
Transient cardiac apical ballooning syndrome
Transient left apical ballooning syndrome
Transient cardiac ballooning
Left apical ballooning syndrome
Acute apical ballooning syndrome

Cardiac apical ballooning syndrome
Apical ballooning
Apical ballooning without apical ballooning
Apical ballooning cardiomyopathy
Reversible apical ballooning of left ventricle
Left ventricular ballooning syndrome
Midventricular variant of transient apical ballooning
Midventricular ballooning syndrome
Transient left ventricular mid-portion ballooning
Transient midventricular ballooning
Transient midventricular ballooning cardiomyopathy
Transient left ventricular nonapical ballooning
Reverse or inverted left ventricular apical ballooning syndrome
Inverted left ventricular apical ballooning syndrome
Transient basal ballooning
Tako-tsubo
Takotsubo cardiomyopathy
Takotsubo-like cardiomyopathy
Takotsubo syndrome
Takotsubo disease
Takotsubo left ventricular dysfunction
Takotsubo-like left ventricular dysfunction
Takotsubo-like transient biventricular dysfunction
Takotsubo-like transient left ventricular ballooning
Takotsubo-shaped cardiomyopathy
Takotsubo-shaped hypokinesia of left ventricle
Takotsubo-type cardiomyopathy
Takotsubo transient left ventricular apical ballooning
Midventricular takotsubo cardiomyopathy
Midventricular form of takotsubo cardiomyopathy
Inverted takotsubo contractile pattern
Inverted takotsubo cardiomyopathy
Inverted takotsubo pattern
Atypical takotsubo cardiomyopathy
Reverse takotsubo syndrome
Atypical basal type takotsubo cardiomyopathy
Stress cardiomyopathy
Acute stress cardiomyopathy
Human stress cardiomyopathy
Acute and reversible cardiomyopathy provoked by stress
Stress-induced cardiomyopathy
Stress-induced takotsubo cardiomyopathy
Stress-induced apical ballooning syndrome
Stress-related left ventricular dysfunction
Stress-related cardiomyopathy
Stress-related cardiomyopathy syndrome

Stress takotsubo cardiomyopathy
Emotional stress-induced ampulla cardiomyopathy
Midventricular stress cardiomyopathy
Atypical transient stress-induced cardiomyopathy
Stress-induced myocardial stunning
Emotional stress-induced takotsubo cardiomyopathy
Stress-associated catecholamine-induced cardiomyopathy
Neurogenic stress syndrome
Other
Neurogenic stunned myocardium
Adrenergic cardiomyopathy
Broken heart syndrome
Ampulla cardiomyopathy
Ampulla-shaped cardiomyopathy
"Chestnut-shaped" transient regional left ventricular hypokinesia
Ball-shaped spherical dilation of left ventricular apex
The artichoke heart
Transient midventricular akinesia
Transient antero-apical dyskinesia

Reproduced from Sharkey et al. Why not just call it tako-tsubo cardiomyopathy: a discussion of nomenclature. J Am Coll Cardiol 2011;57:1496-1497, with permission from Elsevier.

Table 1. Names Tabulated From Published Reports

2. History

In 1990, Sato and colleagues (6) first described a reversible cardiomyopathy as "tako-tsubo-like left ventricular dysfunction." One year later, Dote and colleagues (7) reported 5 patients with a novel, acute cardiac condition characterized by distinctive regional left ventricular LV systolic dysfunction and transient LV apical ballooning in the absence of significant coronary artery disease. Other Japanese investigators were intrigued by the unusual end-systolic shape of the LV, which resembled the "tako-tsubo," (a fisherman's pot with a round bottom and narrow neck used for trapping octopuses) (2,8,9) (Figure 1). Consequently, the term takotsubo was introduced to describe a new cardiomyopathic syndrome characterized by reversible LV systolic dysfunction (3). Many reports were published from different countries afterwards, and it was first reported in the United States in 2004 (5). A search for the term "takotsubo cardiomyopathy" in MEDLINE returned 1,090 articles (Figure 2).

3. Epidemiology

A few case reports were published prior to 2000, but the recognition of takotsubo cardiomyopathy has increased gradually since 2001, and this condition probably accounts for 1% to 2% of all cases of suspected acute myocardial infarction (MI) (10,11). Given the relatively recent recognition of TTC, epidemiology of this condition is still emerging. TTC is reported to occur predominantly in postmenopausal women (82-100%) (12) soon after exposure to sudden, unexpected emotional or physical stress. Kushiro and colleagues

reported CD36 deficiency in a patient with stress-induced cardiomyopathy (13), suggesting an association between this entity and certain genetic profiles. This observation has led to the speculation that TTC might have a genetic component as described in a report by Cherian and colleagues (14).

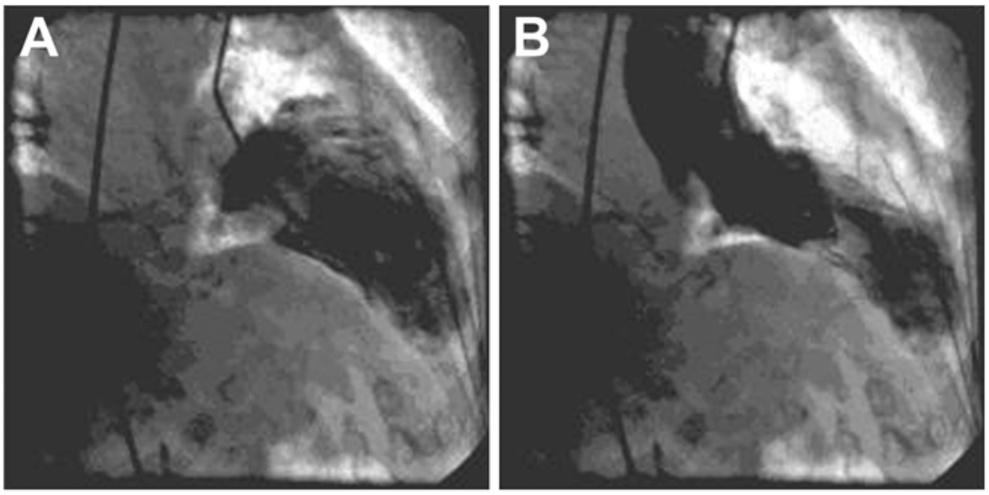

Fig. 1. Left ventriculograms obtained in a 65-year-old female who presented with acute shortness of breath. Panel A is a right anterior oblique (RAO) view of the left ventricle in the diastolic frame. Panel B is the RAO view of the left ventricle in the systolic frame. Note the dilated apical and akinetic outpouching of the left ventricle in Panel B. The coronaries in this patient were normal, consistent with the diagnosis of takotsubo cardiomyopathy.

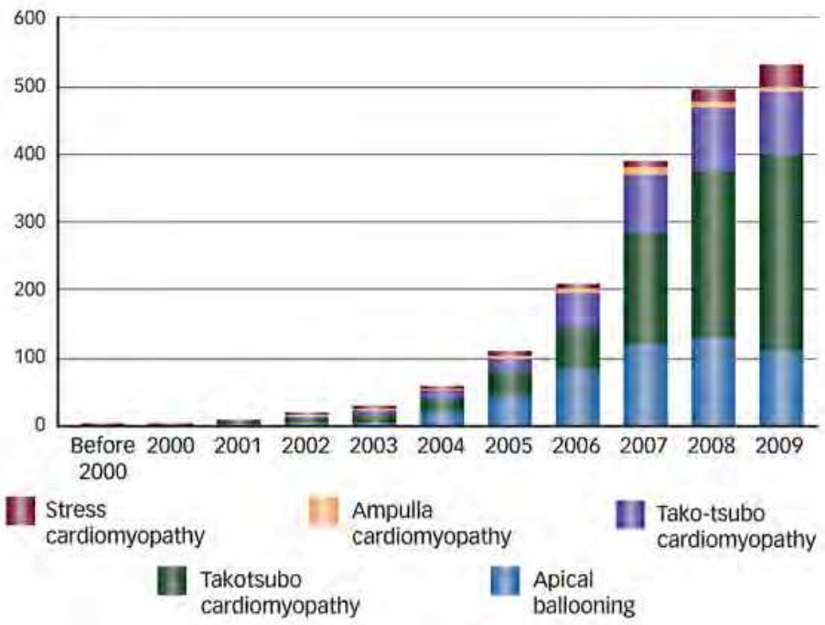

Fig. 2. Increase in the number of publications on MEDLINE® concerning takotsubo cardiomyopathy. (Originally published in *Asia-Pacific Cardiology* 2011;3:60-3. ©Touch Briefings. Reprinted with permission.)

4. Clinical presentation

4.1 The patient

TTC has characteristically been reported in women, with a median age varying from 61 to 76 years in prior case series (2,9,11,15-21). All large-cohort reports of TTC have shown that most patients presenting with the syndrome are postmenopausal women (5). However, it has also been reported in men and patients <50 years (1,3,15,16) and even in a 2-year-old girl (22). In the first large Japanese series describing TTC, 76 patients were women, 12 were men, and the median age was 67 ± 13 years (2).

4.2 The triggering event

Different stresses prior to presentation have been reported to trigger TTC, but the common theme is a sudden physical or emotional stress. The numerous events precipitating TTC are depicted in Table 2. Recurrence of TTC has also been rarely reported with similar or different triggering events (recurrence range, 0 to 8%) (23). TTC has been reported to be associated with pheochromocytoma (24-27) and subarachnoid hemorrhage (28-31) in some published reports.

Emotional stress
Death or severe illness or injury of a family member, friend, or pet
Receiving bad news—diagnosis of a major illness, daughter's divorce, spouse leaving for war
Severe argument
Public speaking
Involvement with legal proceedings
Financial loss—business, gambling
Car accident
Surprise party
Move to a new residence
Physical stress
Non-cardiac surgery or procedure—cholecystectomy, hysterectomy
Severe illness—asthma or chronic obstructive airway exacerbation, connective tissue disorders, acute cholecystitis, pseudomembranous colitis
Severe pain—fracture, renal colic, pneumothorax, pulmonary embolism
Recovering from general anesthesia
Cocaine use
Opiate withdrawal
Stress test—dobutamine stress echo, exercise sestamibi
Thyrotoxicosis

Reproduced from Prasad et al. Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): A mimic of acute myocardial infarction. Am Heart J 2008;155:408-17, with permission from Elsevier.

Table 2. Stressors Reported to Trigger Takotsubo Cardiomyopathy

4.3 The syndrome

The characteristic clinical syndrome is acute LV dysfunction (10). Patients usually present with typical chest pain (70-90%) and dyspnea (20%) (10); other less common presentations include syncope (12), pulmonary edema and cardiac arrest. Dynamic electrocardiographic changes and elevated cardiac biomarkers (reflecting acute myocardial injury) are usually present. Coronary angiography, however, does not reveal any evidence of epicardial coronary obstruction. Left ventriculography (Figure 1) reveals LV dysfunction and wall motion abnormalities affecting apical and, frequently, midventricular myocardium but sparing the basal myocardium, changes which resemble a flask with a narrow neck and a round bottom shaped like the Japanese octopus trap "*tako-tsubo*" (32). Symptoms can be severe and lead to death in 2% of patients (3). Song and colleagues reported 32% (n=16) of their patients with TTC (n=50) presented with cardiogenic shock as initial presentation (33). Table 3 shows clinical features in a prior published series (10).

4.4 Electrocardiography

Most common electrocardiographic changes reported in TTC are ST-segment elevations in precordial leads (10) on admission (range, 46-100% of patients) (12). Subsequent deep symmetrical T-wave inversion in multiple leads and Q-wave formation (range, 6-31% of patients) (12) also are frequently found (10). Also present may be QT interval prolongation (5) (range, 450-501 ms) (12). The combination of clinical symptoms and electrocardiographic changes at patient's initial presentation makes differentiation of TTC from ACS very difficult. A typical electrocardiogram obtained in one of our patients at presentation and 48 hours later is shown in Figure 3.

4.5 Cardiac biomarkers

Most patients present with elevated cardiac biomarkers and have a modest peak in levels within 24 hours (15,19,34), but levels are markedly lower than would be anticipated on the basis of the extent of wall motion abnormalities and electrocardiogram findings (1).

4.6 Left ventriculography

Diagnosis of TTC is frequently made in the cardiac catheterization laboratory during left ventriculography as the patients are initially triaged as an ACS and are referred for urgent or emergency coronary angiography (35). Left ventriculography (Figure 4) reveals the classic appearance of left ventricle with dilated apex and akinetic apical or midventricular walls (or both) and a hypercontractile basal segment. However, more variants of TTC have been reported with diversity in patterns of regional LV systolic dyssynergy. Singh and colleagues (36) reported a series of 107 patients (age=66 ± 14 years, n=99 females) and observed the regional contractility phenotypes shown in Table 4. A study by Kurowski and colleagues (n=35 patients) identified 60% of patients to be typical (apical) and 40% to be atypical (midventricular) variants (11). Subclassifying TTC variants with different names should be avoided as it can lead to more confusion (3). The proposed alternate names – "transient ballooning syndrome" (37) or "transient stress-induced left ventricular dysfunction syndrome" – seem to capture the essential features of the disease, though takotsubo cardiomyopathy remains the most widely used.

	Tsuchihashi et al	Kurowski et al	Kurisu et al	Sharkey et al	Wittstein et al	Inoue et al	Sato et al	Bybee et al	Yoshida et al	Akashi et al
Subjects, n	88	35	30	22	19	18	16	16	15	13
Country	Japan	Germany	Japan	U.S.	U.S.	Japan	Japan	U.S.	Japan	Japan
Series, type	Retro	Pro	Retro	Pro	Pro	Retro	Retro	Pro	Pro	Pro
Age, y	67 ± 13	72 ± 9	70 ± 8	65 ± 13	61 ± 15	76 ± 8	71 ± 9	71 ± 12	72 ± 7	73 ± 10
Women, %	86	94	93	91	95	94	94	100	80	85
Preceding emotional stressor, %	20	42	17	86	100	11	…	38	40	31
Preceding stressor, %	43	42	17	14	…	39	100	4	40	69
Chest pain, %	67	…	67	91	95	72	100	69	87	54
ST-segment elevation, %	90	69	100	59	11	100	56	81	87	92
ST-segment elevation in precordial leads, %	85	…	97	59	…	100	…	81	…	92
Q waves, %	27	…	…	45	37	56†	…	31	7	…
Mean QTc, ms	…	…	…	…	542*	…	…	501 ± 55	508*	…
Elevation in cardiac enzymne leads, %	56	…	…	…	…	…	56	100	…	85
Initial average LVEF	0.41 ± 0.11	0.5 ± 0.13	0.49 ± 0.12	0.29 ± 0.09	0.20*	…	0.49 ± 0.04	0.4	0.43 ± 0.08	0.42 ± 0.10
Follow-up LVEF	0.64 ± 0.10	0.68 ± 0.12	0.69 ± 0.12	0.63 ± 0.06	0.60*	…	0.66 ± 0.03	0.6	0.76 ± 0.01	0.65 ± 0.08
Time of recovery, d	…	…	11.3 ± 4.3	24 ± 29	21*	…	17.7	8	11 ± 4	17 ± 7
Initial Forrester subset	…	…	…	…	…	…	…	…	…	1.9 ± 0.3
Pulmonary edema, %	22	…	3	0	16	28	6	44	…	0
Coronary stenosis >50%, %	0	0	0	0	5	0	0	0	…	0
Angiographically normal coronary arteries, %	…	0	83	100	95	100	100	25	100	100
Spontaneous multivessel spasm, %	0	0	10	…	0	0	0	0	0	0
Provacable multivessel spasm, n/ n (%)	5/ 48 (10)	…	6/ 14 (43)	…	…	…	0/ 6 (0)	…	1/ 6 (17)	0/ 11 (0)
Transient intraventricular pressure gradient, %	18	…	…	23	…	…	…	13	14	…
In-hospital mortality, %	1	3 (9)	0	0	0	6	0	0	0	8
Documented recurrence, n/ n (%)	2/ 72 (3)	2 (6)	0	2/ 22 (9)	0	…	…	1/ 16 (6)	…	0

LVEF indicates left ventricular ejection fraction; Retro, retrospective; Pro, prospective. Values are expressed as mean ± SD when appropriate.

*Median.

†In precordial leads.

Adapted from Gianni et al. Apical ballooning syndrome or takotsubo cardiomyopathy: a systematic review. Eur Heart J 2006;27:1523–1529, with permission from Oxford University Press.

Table 3. Patient Clinical and Laboratory Characteristics

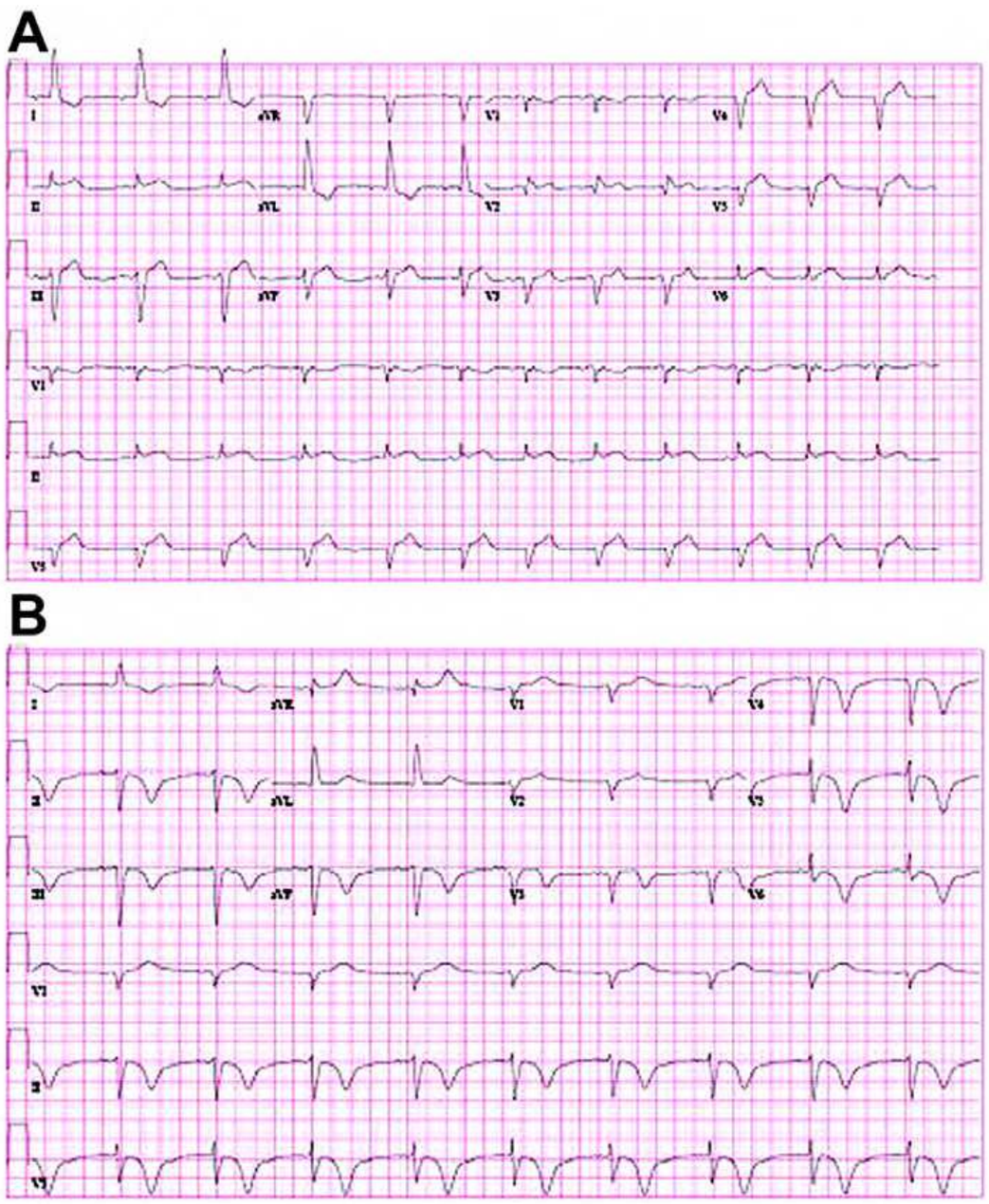

Fig. 3. Electrocardiogram (ECG) changes in one of our patients with takotsubo cardiomyopathy. Panel A: ECG at presentation revealed a 1-mm elevation in V3 and V4 and a new-onset left bundle branch block. Panel B: ECG at 48 hours after presentation revealed T-wave abnormalities in multiple leads.

Posterobasal	1%
Basal + midventricular	1%
Diaphragmatic	2%
Localized apical	2%
Anterolateral	11%
Complete midventricular	29%
Classical takotsubo cardiomyopathy	54%

Data compiled from Singh et al.[36]

Table 4. Variants of Takotsubo Cardiomyopathy[36]

4.7 Coronary angiography

Coronary angiography on presentation fails to reveal any coronary obstruction or acute plaque rupture. However, patients with coronary artery disease can develop TTC. Kurisu and colleagues (38) reported 10% of patients in their series of takotsubo patients (total patients=97) had >75% coronary artery obstruction in a major coronary vessel, though coronary stenosis is uncommon in patients presenting with TTC (1), and absence of an acute coronary artery syndrome is a diagnostic criterion for diagnosis of TTC.

4.8 Echocardiography

Echocardiography also plays a pivotal role in the diagnosis of TTC. This is particularly so given the ability to rapidly perform bedside echocardiography with echo-Doppler imaging. Accurate evaluation by echocardiography, particularly after coronary evaluation by catheterization, can assist in further defining the diagnosis, particularly, when echocardiography repeated after few days to weeks shows complete normalization of regional wall motion abnormalities and LV ejection fraction. Typically, TTC appears like an evolving acute anterior wall myocardial infarction (MI) with akinesia of the apex, apical anterior wall and septum (Figure 5). Left ventricular outflow tract obstruction, a transient phenomenon in TTC, can also be recognized by echocardiography.

In contemporary clinical practice, three-dimensional speckle tracking echocardiography (3D-STE) can be used to assess myocardial mechanical function. It permits the calculation of complex myocardial mechanical parameters such as strain and strain rate, rotation, torsion, as well as LV volume and ejection fraction in three dimensions within minutes. It has been validated against sonomicrometry, magnetic resonance imaging (MRI) tagging, and found to be more accurate and reproducible than two-dimensional speckle tracking echocardiography (2D-STE). We have observed that the global longitudinal, circumferential and radial strains are all decreased significantly in acute anterior wall myocardial infarction and TTC in the acute phase. However, regional circumferential and radial strains at mid and apical LV are significantly lower in TTC patients than in acute anterior wall MI.

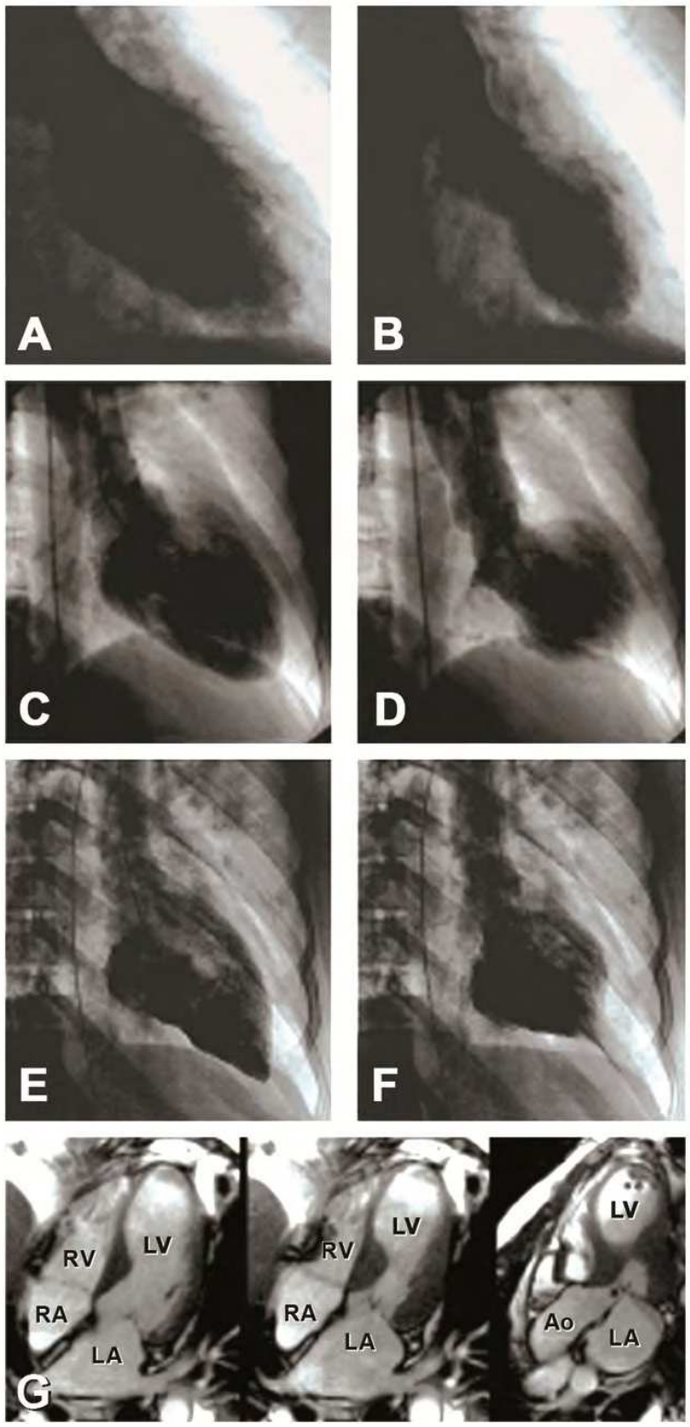

Fig. 4. Radiograph of the left ventricle. (A) Left ventriculogram in diastole. (B) Left ventriculogram in systole shows preserved contraction of the base of the ventricle and apical ballooning. (C) Right anterior oblique view in diastole. (D) Right anterior oblique view in systole. Note the hypercontractility of the basal and apical segments and ballooning of the midventricular segments. (E) After methamphetamine use in end-diastole. (F) After

methamphetamine use in end-systole. Basal segments are akinetic, the papillary level shows normal contractility, and the apex is hypercontractile. (G) Cardiac magnetic resonance image. Hypotension may be due to dynamic outflow tract obstruction caused by hyperkinesis of the basal left ventricle segments and systolic anterior motion of the mitral valve. Four-chamber, steady-state, free-precession image: end-diastole (left) and end-systole (center) show left and right ventricular apical akinesis. (Right) Three-chamber image in systole shows systolic anterior motion of the mitral leaflets (*) with dynamic left ventricular outflow tract obstruction; left ventricular apical mass consistent with thrombus (**). Ao = aorta; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle. (Panels A and B are adapted from Hurst et al. Takotsubo cardiomyopathy: A unique cardiomyopathy with variable ventricular morphology. JACC: Cardiovascular Imaging 2010;3:641-9, with permission from Elsevier. Panels C and D are adapted from Hurst et al. Transient midventricular ballooning syndrome: a new variant. J Am Coll Cardiol 2006;48:579-83, with permission from Elsevier. Panels E and F are adapted from Reuss et al. Isolated left ventricular basal ballooning phenotype of transient cardiomyopathy in young women. Am J Cardiol 2007;99:1451-3, with permission from Elsevier. Panel G is adapted from Syed et al. Apical ballooning syndrome or aborted acute myocardial infarction? Insights from cardiovascular magnetic resonance imaging. Int J Cardiovasc Imaging 2008;24:875-82, with permission from Springer.)

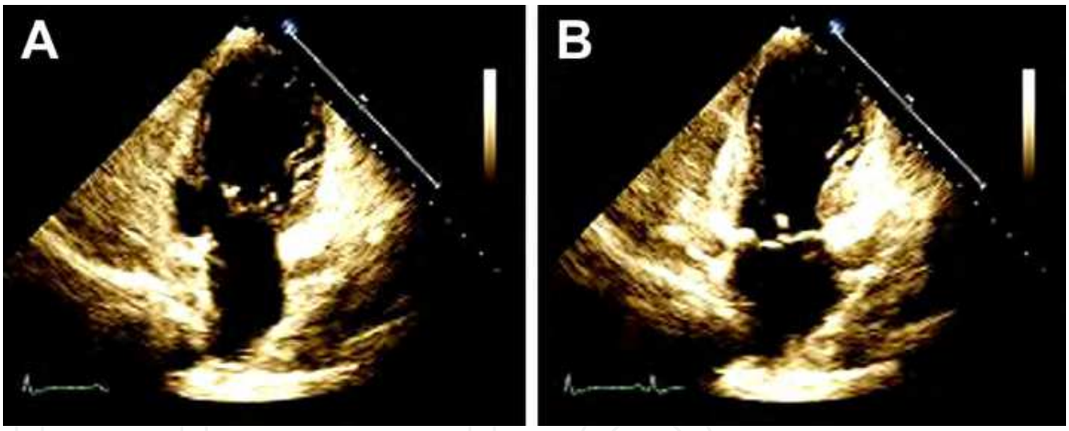

Fig. 5. Two-chamber view of the left ventricle, obtained in diastole (Panel A) and systole (Panel B), in a 56-year-old female who presented to the hospital in florid pulmonary edema after witnessing a car accident. Panel B demonstrates the akinetic and balloon apex in systole with a hypercontractile base, a classic variant of takotsubo cardiomyopathy.

4.9 Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging may be helpful in differentiating TTC from MI and myocarditis. TTC is characterized by the absence of delayed gadolinium enhancement, whereas MI is characterized by subendocardial delayed hyperenhancement and myocarditis is characterized by patchy delayed hyperenhancement (39-41). Cardiac magnetic resonance can also demonstrate the typical bulging of the LV apex and hypercontractile function of the base with accurate rendering of the LV stroke volume. It can also demonstrate the presence of LV thrombus in akinetic apex (Figure 6).

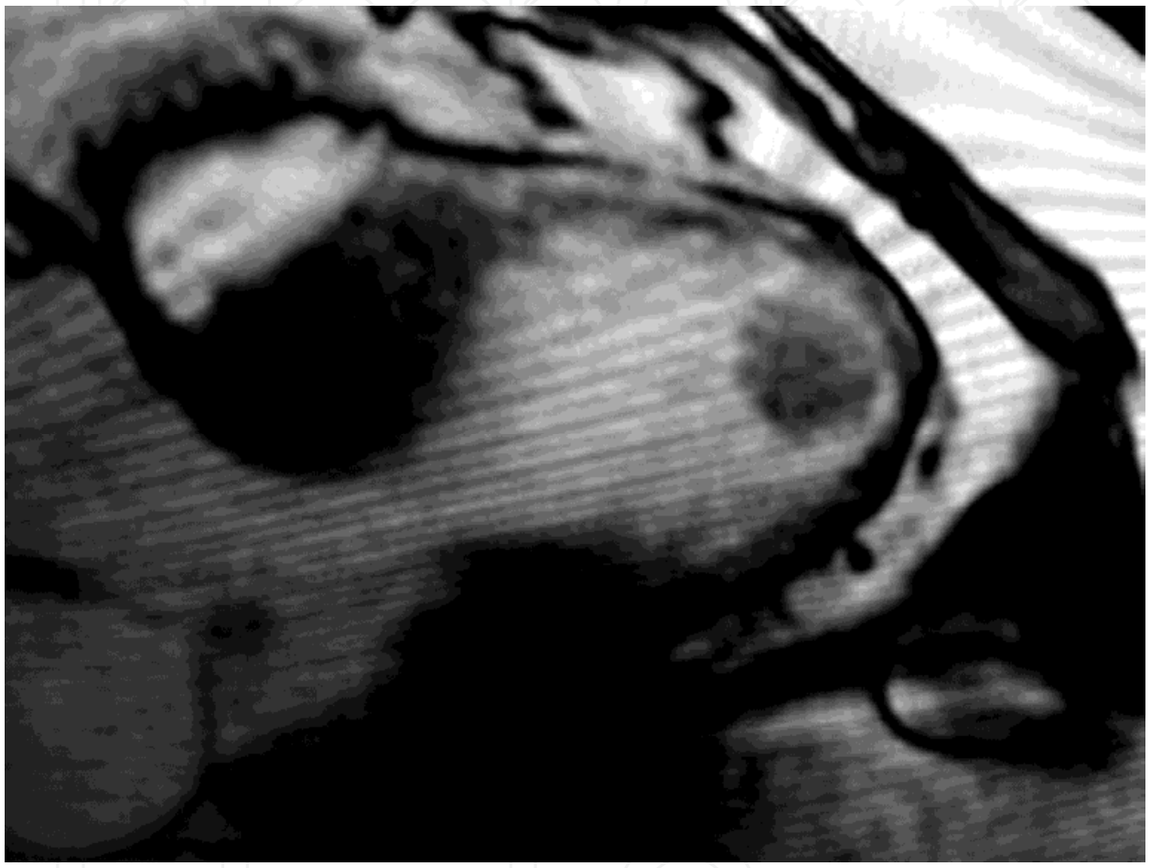

Fig. 6. Two-chamber Fast Imaging Employing Steady-State Acquisition (FIESTA) motion sensing in a 76-year-old female who presented to the hospital with chest pain and shortness of breath after witnessing an acute asthma attack in her grandchild. The figure demonstrates left ventricular apical bulging and a hypercontractile base with a 1.5 × 1.5-cm thrombus within the left ventricular apex.

4.10 Clinical outcome and prognosis

A complete recovery of LV wall motion abnormalities is a hallmark of this syndrome in virtually all patients (2,15,16,35). Recovery time varies, from as short as several days to as long as 4-8 weeks, and is a requirement for the diagnosis (15). The diagnostic criteria are summarized in Table 5.

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 coronary disease 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.
4. Absence of:
   Pheochromocytoma
   Myocarditis

In both of the above circumstances, the diagnosis of takotsubo cardiomyopathy should be made with caution, and a clear stressful precipitating trigger must be sought.
*There are rare exceptions to these criteria such as those patients in whom the regional wall motion abnormality is limited to a single coronary territory.
†It is possible that a patient with obstructive coronary atherosclerosis may also develop takotsubo cardiomyopathy. However, this is very rare in our experience and in the published literature, perhaps because such cases are misdiagnosed as an acute coronary syndrome.
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Table 5. Proposed Mayo Clinic Criteria for Takotusbo Cardiomyopathy

The overall prognosis of TTC appears to be favorable in patients who survive the initial acute phase of heart failure. In-hospital mortality has been reported between 0 and 8% (12). Reported complications associated with TTC are left heart failure with and without pulmonary edema, cardiogenic shock, dynamic intraventricular obstruction with left ventricular intracavitary pressure gradient generation, mitral regurgitation resulting from chordal tethering as well as systolic anterior motion of the mitral valve apparatus, ventricular arrhythmias, LV mural thrombus formation, left ventricular free-wall rupture and death (12). Cardiogenic shock (6.5%), congestive heart failure (3.8%) and ventricular tachycardia (1.6%) are other known complications, while ventricular fibrillation, LV mural thrombus formation, ventricular septal defect, LV free wall rupture and pneumothorax have infrequently been reported (12,37).
Recently, Madhavan and colleagues (42) have proposed the "Mayo Clinic Risk Score" system for acute heart failure in TTC (Table 6). The scoring system was developed to predict which patients with TTC are at risk of developing systolic heart failure. Presence of 1, 2 and 3 points was associated with 28%, 58% and 85% risk of acute heart failure.

Risk Factor	Score
Age > 70 years	1
Presence of physical stressor	1
Ejection fraction < 40%	1

Table 6. Proposed Mayo Clinic Risk Scoring System of Acute Heart Failure in Takotsubo Cardiomyopathy

5. Pathogenesis

The aphorism "a broken heart" is well known to be associated with emotional stress by the lay person. Association of TTC with acute emotional and physical stress lends a scientific basis for this observation. But the exact underlying mechanism still proves elusive. Due to the recent recognition of TTC and its low incidence of diagnosis, as mentioned earlier, only a relatively small number of patients have been studied in a few published series. No large studies have confirmed the etiology of TTC (43). A rapidly accumulating body of evidence has led to very interesting insights into the possible pathophysiology of TTC. Most current hypotheses are based on cathecholamine surges in the setting of acute emotional or physical stress leading to catecholamine-related cardiac toxic effects (32,44-49) and was first suggested by Wittstein and colleagues (16). In this section we examine various advancements in understanding TTC pathophysiology.

5.1 Obstruction of the left ventricular outflow tract

Early investigators observed left ventricular outflow tract (LVOT) obstruction in some patients presenting with TTC. Villarreal and colleagues hypothesized that patients with a sigmoid interventricular septum, small LVOT, reduced LV volume (primarily elderly women) and an abnormal orientation of a slack mitral apparatus have a geometric predisposition to dynamic LVOT obstruction, which may manifest in the setting of intense adrenergic stimulation or hypovolemia (50,51). Elderly females seem to have a higher incidence of basal septal thickening (52), and this could become a substrate for LVOT obstruction leading to severe, transient midcavity obstruction in the setting of a cathecholamine surge (53). LVOT obstruction may cause or worsen hypotension due to LV systolic dysfunction by contributing to significant mitral regurgitation secondary to systolic anterior motion of mitral valve and dynamic LVOT obstruction (54). Presence of LVOT may change the management of TTC patients and is detailed in the treatment section of this chapter. However, incidence of LVOT obstruction in patients presenting with TTC in various studies has varied from 11-25% of patients (12,52,55) and is not observed in all patients. Its role in the pathogenesis of TTC is unclear, and it remains uncertain if LVOT obstruction is a cause or a consequence of TTC (49).

5.2 Vasospasm of epicardial coronary arteries hypothesis

Clinical presentation of TTC bears close resemblance to an acute MI. Therefore, early hypotheses speculated that an ischemic event triggered by transient coronary plaque rupture (56) or reversible coronary vessel spasm (7) was responsible for "stunning" the ventricle. A few authors reported finding a long left anterior descending artery (LAD) that

wrapped around the apex in their patients presenting with TTC, and it was hypothesized that transient obstruction of epicardial blood flow to the left ventricle in a given coronary bed may lead to the regional akinesis or "ballooning" typically observed in TTC. However, there are multiple problems with such an explanation. For one, the aforementioned coronary artery anatomy is not found on coronary angiography in all patients presenting with TTC. Secondly, spontaneous coronary vasospasm has been reported in only 2% of patients with TTC (12). Furthermore, an acute coronary vessel-obstructing lesion has not been described in patients with TTC immediately after presentation (57) and has been proposed as an exclusion criterion (35) for TTC diagnosis. Thirdly, as mentioned earlier, there are reports of numerous phenotypes of TTC that present with regional hypokinesis that encompasses territories of the left ventricle not supplied by a single vessel (35). Fourthly, histological examination of cardiac tissue in patients with acute MI reveals polymorphonuclear inflammation, whereas TTC is associated with an interstitial mononuclear inflammatory response and considerable increase in extracellular matrix protein and contraction band necrosis—a unique form of myocyte injury characterized by hypercontracted sarcomeres and dense eosinophilic transverse bands associated with catecholamine-excess states like pheochromocytoma and subarachnoid hemorrhage (16,49). Finally, provocative tests with infusion of ergometrine or acetylcholine for inducible coronary vasospasm in patients with TTC were only positive in 28.6% of patients (55) and 27.6% of patients (58) in two published series, respectively. These equivocal results combined with the factors mentioned above make obstruction of blood flow in epicardial coronary vessels seem less likely to explain the pathophysiology of TTC.

5.3 Coronary microvascular blood flow abnormalities

Several investigators (11,19,59) have suggested microvascular dysfunction to be a potential pathophysiologic mechanism in TTC. Kume and colleagues demonstrated microcirculation disturbances in patients with TTC by use of Doppler flow-wire assessment (60). Other investigators have used TIMI (Thrombolysis in Myocardial Infarction) frame counts to assess coronary blood flow. Using this technique, Kurisu (59) and colleagues found significantly higher frame counts in TTC compared to a control group. Bybee and colleagues (19) also found abnormal TIMI frame counts in one or more major epicardial vessels in patients with TTC in their published series. These findings suggest that microvascular integrity in TTC is impaired in all coronary arteries in many patients, and the microvascular dysfunction in LAD is comparable to that of patients with acute anterior ST-segment elevation myocardial infarction after recanalization of the infarct-related artery.

Nuclear studies with single-photon emission tomography (SPET) and fluorodeoxyglucose positron emission tomography (FDG-PET) were performed by Kurowski (11) in their patients with TTC and revealed that myocardial glucose metabolism was more affected than perfusion. The authors concluded that this "inverse mismatch" pattern is similar to that seen in postischemic "stunned" myocardium (61).

These findings indicate that diffuse coronary microvascular dysfunction is present in patients with TTC. However, whether this is an effect or cause of this syndrome is unclear (10). This type of microvascular dysfunction, however, can be a result of a surge in catecholamine secretion, which is described in detail later in this chapter.

5.4 Catecholamine-induced acute myocardial stunning hypothesis

5.4.1 Alterations in calcium handling

Akashi and colleagues were the first to report elevated serum catecholamine levels in patients with TTC (62). Wittstein and colleagues (16) later reported supraphysiologic levels of plasma catecholamines in their series (n=19 patients), which reported plasma levels of epinephrine, norepinephrine and dopamine in patients with TTC to be 2-3 times higher than those of patients with Killip class III MI and 7-32 times higher than the published normal values (63). They also noted higher levels of both neuronal (dihydroxyphenylglycol, dihydroxyphenylglycol and dihydroxyphenylacetic acid) and extraneuronal catecholamines (metanephrine, normetanephrine and neuropeptide Y). In Wittstein's series, the plasma cathecholamine levels trended downward by day 7-9 but still remained elevated. They concluded that TTC was associated with activation of adrenomedullary hormonal system and enhanced sympathoneural activity. Similarly, administration of epinephrine at suprapharmacological doses led to induction of stress cardiomyopathy in two cases (64,65). Several investigators (16,32,66) have suggested direct myocardial stunning as a result of the catecholamine surges. Such a stunning could possibly explain the findings in TTC. Catecholamine-overload state is associated with the following histologic changes: 1.) increased production of extracellular matrix leading to a rapid increase in fibrosis; 2.) contraction band necrosis; and 3.) mild neutrophil infiltration (44). There is increased production of oxygen-derived free radicals (67) that interfere with sodium and calcium transporters, resulting in myocyte dysfunction through increased transsarcolemmal calcium influx and cellular calcium overload (68). Mori and colleagues (69) demonstrated that apical myocardium has a higher concentration of beta-adrenoceptors with a concentration gradient decreasing from apex to base. This could explain the enhanced responsiveness to sympathetic stimulation potentially making the apex more vulnerable to sudden surges in circulating catecholamine levels and, thus, could explain the typical phenotype most commonly found in TTC patients (16).

Investigators have noted disturbance of the calcium regulatory system in stress-induced cardiomyopathy. Some animal models have been shown to describe altered expression of the calcium regulatory system protein genes by supraphysiological levels of catecholamines (70,71) (Figure 7).

Sarcolipin regulates sarcoplasmic/endoplasmic reticulum calcium ATPase2 (SERCA) by lowering its affinity for calcium. Elevated catecholamines in TTC cause increased expression of sarcolipin in the acute phase, leading to reduced affinity of SERCA2 for calcium (49,72,73). Elevated levels of catecholamines also lead to reduced expression of SERCA2 messenger RNA levels through intense G-protein-stimulated β1 and β2 adrenergic receptor signaling in animal models (74). The G-protein-stimulated β1-adrenergic receptor and α1-adrenergic receptor can directly modulate SERCA2 gene expression (via cyclic AMP-responsive element binding protein 1 and calcineurin-nuclear factor of activated T cells signaling pathways) (75). Excessive adrenergic signaling could thus explain the cardiotoxicity observed in patients with stress cardiomyopathy from cardiomyocytes calcium overload, mitochondrial calcium overload, reactive oxygen species production and oxidative stress (32,49). However, there is no evidence to suggest that alterations in expression of calcium-handling proteins are responsible for the acute deleterious effects of TTC (49).

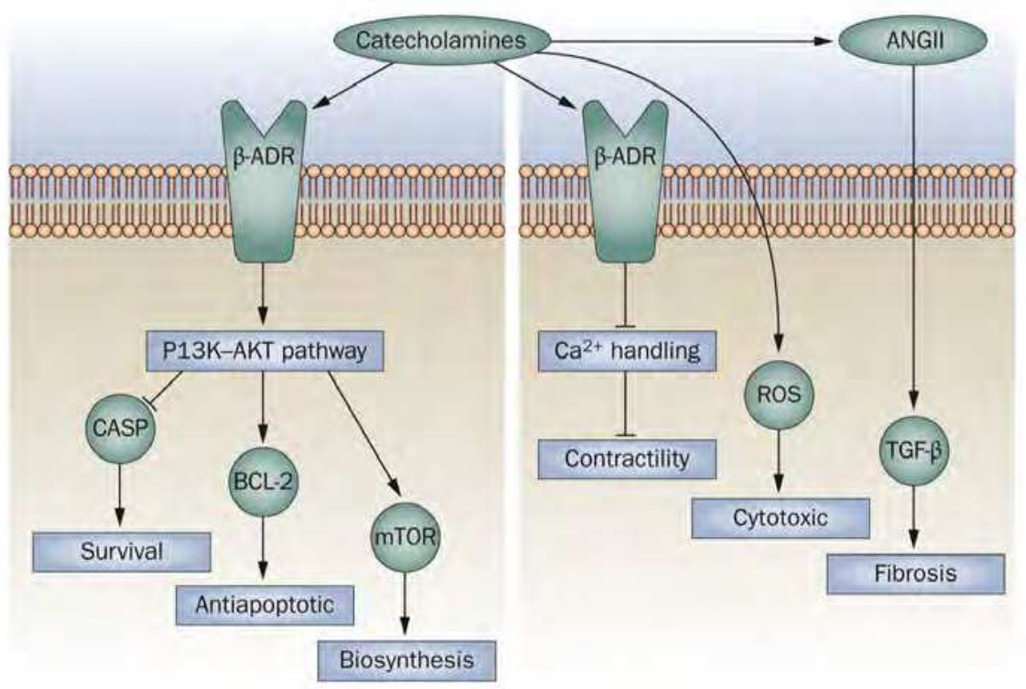

Fig. 7. The pathomechanistic concept of stress cardiomyopathy. Overexpression of catecholamines following a stress event leads to a number of changes that can have either protective or adverse effects. Abbreviations: β-ADR, β-adrenergic receptor; ANGII, angiotensin II; CASP, caspase; mTOR, mammalian target of rapamycin; PI3K–AKT, phosphatidylinositol 3 kinase–AKT; ROS, reactive oxygen species; TGF-β, transforming growth factor β. Reproduced from Nef et al. Mechanisms of stress (Takotsubo) cardiomyopathy. Nat Rev Cardiol 2010;7:187–193, with permission from Nature Publishing Group.

5.4.2 Stimulus trafficking

5.4.2.1 Stimulus trafficking causes negative inotropism

Human ventricular cardiomyocytes have two types of β-adrenergic receptors (AR), β1 and β2, but the concentration of β2 is higher than β1 (4:1) (76). At physiological and elevated concentrations, norepinephrine and epinephrine act via β1-AR exerting positive inotropic and lusitropic responses through coupling with the Gs protein family. Epinephrine has higher affinity for β2-AR and activates the Gs protein family, causing positive inotropic response. However, at supraphysiological levels, epinephrine stimulates a negative inotropic effect (77) by causing a switch from β2-AR Gs protein signaling to β2-AR Gi protein signaling (78), a process called stimulus trafficking (32). Intense activation of the β1-AR Gs protein and β2-AR Gs protein pathways is thought to initiate the switch in signal trafficking from β2-AR Gs protein to β2-AR Gi protein coupling (79). The Gi protein pathway exerts a negative inotropic effect through multiple pathways (32).

After the surge in epinephrine levels has cleared from the circulation, negative inotropy-causing β2-ARs that are coupled to Gi proteins either switch back to Gs protein coupling or are internalized and degraded, enabling cardiomyocytes to recover their inotropic function.

This sequence of events would explain the reported recovery of ventricular function in individuals with stress cardiomyopathy (32).

5.4.2.2 Typical TTC phenotype explained by stimulus trafficking

In human hearts, the density of the sympathetic nerve endings is approximately 40% greater at the base compared to the apex (80), whereas the concentration of β-ARs is higher in the apical myocardium (69). It has been proposed that the concentration of β-ARs in the apical myocardium is increased to compensate for the decrease in the direct sympathetic innervation, thereby maintaining a balanced responsiveness of the ventricle-to-sympathetic drive (32). Thus, the apex might be more sensitive and responsive to circulating catecholamines. An increasing density of β2-ARs from the base to the apex could explain the regional difference in response to high catecholamine levels, with circulating epinephrine having a greater influence on apical function, relative to basal function.

5.5 Atypical phenotype

Certain factors can influence the local epinephrine concentration in the myocardium. A study in rabbits demonstrated conversion of norepinephrine to epinephrine by phenylethanolamine N-methyltransferase in the ventricular myocardium (81). Thus, regional differences in epinephrine concentrations can play a role in responsiveness of the myocardium to catecholamines and could explain atypical phenotypes observed in some TTC patients (32).

5.6 Female predominance related to hormones

Some investigators have suggested reduction of estrogen levels in postmenopausal females to be one of the underlying factors of TTC.

Estrogen receptors are expressed on cardiomyocytes (82), thus cardiomyocyte function could be directly affected by estrogen levels. Estrogen has also been shown to significantly suppress SERCA2 expression in ovariectomized rats compared to controls, thus altering cardiac myocyte sarcoplasmic reticulum calcium uptake (83). In the latter study, investigators noted that estrogen and progesterone supplementations were equally effective in preventing changes in ovariectomized hearts.

Men rarely develop stress cardiomyopathy yet are physiologically estrogen-deficient, which suggests that this syndrome is not due to ovarian hormone deficiency. However, effects of hormone deficiency on contractility in the presence of excessive catecholamine levels need further clarification (49).

5.7 Possible familial link

Burgdorf and colleagues (84) recently reported a series of 144 patients with TTC (107 typical cases and 34 atypical cases) in which 26 patients were known to have cancer, while 7 patients were newly diagnosed with cancer. On basis of this observation, they proposed that an association between cancer and TTC cannot be excluded and that patients diagnosed with TTC should undergo screening for cancer. While there might be an association, one possible confounder could be the neurally mediated hypothesis of stress associated with learning about the diagnosis of cancer.

6. Treatment

TTC is a self-limiting syndrome; cardiac function returns to pre-TTC levels within a few weeks and patients carry a favorable prognosis (2). However, patients require standard supportive treatment during the acute phase. This treatment is similar to a congestive heart failure treatment regimen with diuretics and vasodilators (16). Vasopressors and beta-agonists should be avoided due to catecholamine-surplus state. Also, epinephrine administered may drive further β2-AR, Gi protein-mediated negative inotropism (32). Use of β-blockers should be carefully considered as some β-blockers can also cause stimulus trafficking of β2-ARs to Gi protein coupling (85), which, in the acute phase of TTC, can lead to further suppression of LV function. However, in the long term, β2-AR/Gi coupling may enhance the ability of β-blockers to protect and improve the function of the failing heart (85). Mechanical circulatory support in patients with intraaortic balloon counter pulsation (IABP) is appropriate to avoid vasopressor support in these patients (16). Administration of intravenous calcium or levosimendan (a calcium-sensitizing agent) has also been suggested as the inotrope of choice in TTC patients (86,87), but has not been clinically validated in any major study. Some investigators have used it to avoid IABP in TTC patients (88). In patients with moderate to severe hemodynamic compromise and echocardiographic evidence of significant LVOT obstruction (with a dynamic gradient possibly accompanied by systolic anterior motion of mitral valve), both IABP counter pulsation and inotropes are relatively contraindicated because they could worsen the dynamic gradient and thereby further jeopardize cardiac function (54,89); treatment should instead be more conservative with careful fluid management to avoid excessive preload reduction, β-blockers if tolerated (to increase diastolic filling time and thus end-diastolic volume) and occasionally peripheral vasoconstrictors (54,90,91). Finally, in patients with life-threatening acute left ventricular failure, temporary use of a LV assist device may be required (32).

7. Conclusion

Takotsubo cardiomyopathy is a unique form of transient nonischemic stress-induced cardiomyopathy. A well-recognized syndrome now, two decades after its first reported case, it is also being reported in populations other than postmenopausal women. Even though apical ballooning phenotype is the most common and typical presentation, much confusion has resulted from various nomenclatures being used for different presentations of this syndrome. The underlying mechanism is not fully understood but could be common and explained by changes in molecular pathways like *stimulus trafficking* under supraphysiological levels of catecholamines, and influenced by hormonal status. Clinical history, electrocardiogram and diagnostic imaging with coronary angiography and/or cardiac magnetic resonance imaging that establishes typical phenotypic features of the disease in absence of significant obstructive coronary artery disease are essential for diagnosis and to differentiate it from an acute myocardial infarction. Management focuses on supportive care in the acute phase, while avoiding vasopressor medications. Mortality is low if patients survive the initial critical period and, by definition, they go on to have a full recovery. Recurrence has been reported but is rare. More studies are needed to fully understand the underlying mechanisms.

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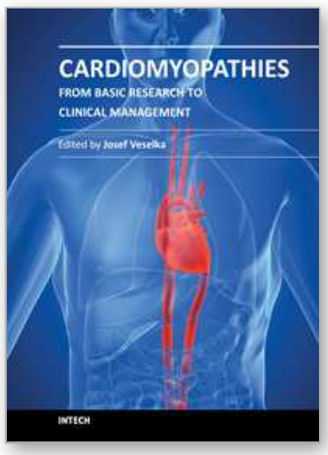

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Cardiomyopathy means "heart (cardio) muscle (myo) disease (pathy)". Currently, cardiomyopathies are defined as myocardial disorders in which the heart muscle is structurally and/or functionally abnormal in the absence of a coronary artery disease, hypertension, valvular heart disease or congenital heart disease sufficient to cause the observed myocardial abnormalities. This book provides a comprehensive, state-of-the-art review of the current knowledge of cardiomyopathies. Instead of following the classic interdisciplinary division, the entire cardiovascular system is presented as a functional unity, and the contributors explore pathophysiological mechanisms from different perspectives, including genetics, molecular biology, electrophysiology, invasive and non-invasive cardiology, imaging methods and surgery. In order to provide a balanced medical view, this book was edited by a clinical cardiologist.

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University Campus STeP Ri
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