Pathophysiological Mechanisms of Takotsubo Cardiomyopathy - a Systematic Review

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Abstract

Takotsubo cardiomyopathy, also referred to as stress-induced cardiomyopathy, is an acute condition associated with transient left ventricular dysfunction. Since it can be induced by increased emotional stress (such as losing a loved one or constant anxiety) it is also called the broken heart syndrome. This type of cardiomyopathy occurs in all age groups and both sexes, but it is most common in postmenopausal women. There are several clinical manifestations such as chest pain, sometimes with heart failure, and often with ST-segment changes that may present as acute coronary syndrome. It is characterized by absence of coronary artery obstruction, with transient regional wall motion abnormalities and minimal elevation of cardiac enzyme levels. Although wall motion abnormalities are reversible in almost all cases, and long-term prognosis is excellent, this condition is important because in the acute phase it may cause sudden cardiac death. Mechanisms and cause of this disease still remain unclear. Some possible causes of the disorder include: 1) coronary artery vasospasm, 2) microcirculatory dysfunction, 3) transient obstruction of the left ventricular outflow tract, and 4) excessive release of catecholamine, which seems to have the most important role. The aim of this review is to summarize the most important pathophysiological mechanisms that may be responsible for the development of this type of cardiomyopathy.

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Introduction

Takotsubo cardiomyopathy (TTC), also known as stress-induced cardiomyopathy, is a condition with left ventricular (LV) dysfunction, most commonly apical ballooning and less frequently

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midventricular or basal dysfunction. It was first described by Sato et al. in the early 1990s, who named it Takotsubo because the appearance of the LV is reminiscent of the octopus trap (1). The exact cause of this disease is still unclear. TTC clinically manifests with sudden chest pain and dyspnea preceded by emotional or physical stress, which are similar to those in acute coronary syndrome (ACS). Besides the onset of chest pain, ST-segment elevation and increase in creatine kinase and troponin are very common, and it is necessary to exclude obstructive coronary artery disease (CAD) (2).

Different types of LV wall motion abnormalities have been reported – apical, mid-ventricular or basal hypokinesia, dyskinesia or akinesia. Beside the LV, right ventricle may also be affected and it is associated with more severe LV dysfunction (3). Any form of dysfunction is reversible with resolution achieved in several days or weeks. Overall prognosis is favorable, but acute phase can be accompanied with acute heart failure and cardiogenic shock, rupture of the LV, malignant arrhythmias and in worst cases sudden cardiac death (4). For TTC diagnosis, four diagnostic criteria are suggested: 1) new electrocardiogram (ECG) abnormalities (convex ST-segment elevation); 2) transient apical dyskinesia or akinesia detected by echocardiography (ECHO); 3) non-obstructive CAD at angiography: 4) absence of myocarditis, pheochromocytoma, head trauma and intracranial hemorrhage or hypertrophic cardiomyopathy (5).

The actual incidence of TTC is unknown, but it is considered that prevalence among patients with ACS symptoms is 0.7-2.5%, and it is found most commonly in postmenopausal women (6). Since no large studies have confirmed the etiology of stress cardiomyopathy, determination of underlying cause is not possible, but it is almost always preceded by exaggerated emotional, physical or mental stress. Sudden death of a loved one, traffic accidents, various types of abuse, business failure, endoscopy, sexual intercourse and other are described as potential triggers of TTC. So far, several possible pathological mechanisms have been proposed, including coronary artery vasospasm, coronary microcirculatory dysfunction, myocarditis, obstruction of the left ventricular outflow tract (LVOT), abnormal metabolism of free fatty acids in the cardiac apex and catecholamine overload (7). TTC does not require specific treatment; management is primarily empirical and needs to be individualized for each patient (8).

This review will explain recent findings about the pathophysiological mechanisms in this type of cardiomyopathy.

Clinical Presentation, Diagnosis and Prognosis

Since TTC patients present with chest pain, dyspnea and syncope, it is difficult to differentiate it from ACS based on ECG and laboratory findings. Last findings suggest that approximately 1-2 % of patients presenting as ACS are ultimately identified as TTC (3, 9). There is no age group or sex that cannot be affected, but there is female predominance (more than 80% of patients are postmenopausal women) and it affects older adults more frequently (10-16). Similar to ACS, TTC patients also have cardiovascular comorbidities such as smoking, hypertension and dyslipidemia (17).

TTC is often, but not always, triggered by emotional or physical stress such as receiving bad news, unexpected death of relatives, dissatisfaction with relationships, devastating financial loss or acute medical illness. Some of the physical stressors include major surgeries like trauma surgery, infections or neurologic conditions. Patients with psychiatric or neurologic disorders may be predisposed to stress cardiomyopathy. Virtually any stressor, evena minor one, can be a precipitant of stress cardiomyopathy. It is worth mentioning that no stressor is identified in up to one-third of patients.

Physical findings are nonspecific and often normal, but the patient may present with signs of ACS or acute congestive heart failure. Other symptoms include nausea, vomiting and palpitations. Cardiac bradyarrhythmias and tachyarrhythmias, including ventricular tachycardia and ventricular fibrillation, may

develop. (10, 11, 18-20). Some patients may develop signs of heart failure, and approximately 10% of patients may develop cardiogenic shock (21-23). Left ventricular outflow tract obstruction caused by left ventricular basal hyperkinesis produces late-peaking systolic murmur and can contribute to severe mitral regurgitation, hypotension and shock (24).

Like any patient in whom ACS is suspected, ECG should be the initial test obtained. ECG abnormalities are common in patients with TTC (25). Most common abnormalities on initial ECG are ST-segment elevation and T-wave inversion. Studies found that ST-segment elevations involve the precordial leads and are maximal in leads V2-V3 (26). Patients with TTC have a significantly lower amplitude of ST segment elevation compared to STEMI from LAD occlusion. ST depression is a less common finding in patients with TTC. Kosuge et al. found that combination of absent abnormal Q waves, absent reciprocal changes, lack of ST-segment elevation in lead V1, and the presence of ST-segment elevation in lead aVR had 91% sensitivity and 96% specificity for TTC. Other possible findings include QT interval prolongation and non-specific ECG abnormalities. However, all these criteria have imperfect diagnostic accuracy and are not reliable for differentiation between the two conditions in the emergency setting to guide their management (e.g. decision to undergo emergency coronary angiography) (27).

Serum cardiac troponin I levels (TnI) are elevated in 90% of patients with TTC, while creatine kinase levels are generally normal or slightly elevated. The brain natriuretic peptide (BNP) orN-terminal pro-BNP are elevated in most patients with TTC (25). In patients with TTC, mean TnI level at the time of admission has been reported as moderately elevated. Nascimento et al. used this finding to create a criterion for differentiating between STEMI and TTC (28). The troponin ejection fraction product (TEFP) is the product of the peak troponin I level and the echocardiographically acquired ejection fraction. A TEFP ≥250 had an overall accuracy of 91% for STEMI identification. Budnik et al. found that the NTproBNP / TnI ratio was capable of distinguishing between TTC and STEMI. In this study, the concentration of NTproBNP was greater in patients with TTC than in ones with STEMI, while the concentration of TnI and CKMB mass was higher in the STEMI group than in the TTC group (29). Several studies analyzed the levels of circulating catecholamines in the acute phase and found that 75% of TTC patients had higher levels than patients with STEMI, but their role in diagnosing TTC is unclear (30,31).

Wall motion abnormalities are best identified by echocardiography or left ventriculography. Trans-thoracic echocardiography (TTE) is used as a quick method of diagnosing wall-motion abnormalities typical for TCC (32), such as hypokinesis or akinesis of the mid-segment and apical segment of the LV, which is present in 81.7% of patients (25). Crucially, these wall-motion abnormalities extend beyond the distribution of any single coronary artery. LV ejection fraction was found to be 20-49% on admission. The resolution of TTC usually occurs within four weeks with LVEF improving to 59-76%.

TTC diagnosis is usually confirmed by coronary angiography. Acute presentation with ST-segment elevation and symptoms suggestive of ACS mandate immediate evaluation with coronary angiography to exclude coronary occlusion.

The prognosis in TCM is excellent in most cases, with nearly 95% of patients experiencing complete recovery within 4-8 weeks (13). Mortality estimates range from 1% to 5.9%. Complications occur in around 20% of patients and include LV outflow obstruction, heart failure, ventricular arrhythmias, mitral regurgitation, LV mural thrombus formation or death. International Takotsubo Registry reported 5.9% mortality after 30 days (33). The rate of mortality during long-term follow-up was 5.6% per patient-year. A Swedish registry study found a 30-day mortality of 4.1% in 302 patients with TTC (34). These trials compared mortality in TTC with matched cohorts of patients with acute myocardial infarction or acute coronary syndrome and found a similar risk of death.

Coronary vasospasm and microcirculatory dysfunction

Coronary vasospasm was the first pathophysiological process considered as a cause TTC in the original article by Sato et al. in 1991 (35). Since TTC usually presents with transient wall motion abnormalities ("stunned myocardium") covering the irrigation territories of several coronary arteries (36), a multivessel coronary vasospasm could be the potential cause. However, according to current literature, coronary vasospasm is not a likely cause, because spontaneous vasospasm is rare in these patients (37) and cannot be induced in all the patients during angiography (38). Finally, TTC has a specific histological phenotype which differs from stunning associated with coronary artery disease (39).

On the other hand, there is an increasing body of evidence that microvascular dysfunction is one of potential pathophysiological mechanisms of disease. Diffuse microcirculatory dysfunction could explain wall motion abnormalities (WMAs) in several myocardial regions. Microcirculatory dysfunction may be primary or secondary, i.e. caused by excess of circulating cateholamines (37). The consequence of microcirculatory dysfunction is coronary slow flow (CSF), which in turn causes myocardial WMAs (40). Several methods have been used for evaluating CSF – Doppler guidewire during angiography (41), TIMI (Thrombolysis in myocardial infarction) myocardial perfusion grade (TMPG) (42, 43) and TIMI frame count (TFC) (11,44). The most commonly used method is TFC which is defined as "the number of frames required for the contrast material to travel from coronary ostium to the standardized distal landmark" (44). Several studies have demonstrated an increased TFC (i.e. slower coronary flow) in TTC patients (45-47), which supports the role of microcirculatory dysfunction. A study by Martin et al. in 2013, using peripheral arterial tonometry, demonstrated increased vascular reactivity and decreased endothelial function in response to acute mental stress in patients with previous TTC (48).

Although most of the available literature supports the role of either primary or secondary microcirculatory dysfunction in TTC, it is important to acknowledge that the results are not always uniform. A recent retrospective study by Khalid et al. found the TFC to be higher in left anterior descending (LAD) coronary artery of TTC patients, but no difference was found in TFC in right (RCA) or circumflex (CX) coronary artery (45). This anatomical distribution could explain the most common form of TTC involving the apex and the midventricular subtype, but not the less frequent form which involves the basal myocardium. Sharkey et al., in 2008, found a modest increase in TFC in TTC patients compared to controls (acute anterior STEMI with LAD occlusion), which was statistically significant in LAD and CX, but not in the RCA (30). Abe et al. (2003) found no coronary slow flow, no abnormalities using Doppler guidewire technique and no evidence of viral myocarditis in a series of 17 patients (49). Collste et al. (2015) investigated coronary flow reserve (CFR) by dobutamine stress echocardiography and the authors could not induce microcirculatory dysfunction, but found CFR at low-dose dobutamine was significantly lower in patients with TSC compared to controls (50).

Metabolic Disturbance

One possible hypothesis is that TTC may be considered a metabolic form of cardiomyopathy with disturbed cardiomyocyte metabolism. Several studies that were researching metabolic changes in stunned myocardium found alterations in glucose and fatty acid uptake. Those alterations may be the result of primary metabolic disturbance in cardiomyocyte or due to mitochondrial disturbance (51, 52). The metabolic disturbance was likely linked to the sudden preceding stress and resulted in corresponding perfusion abnormalities.

Yoshida et al. describe abnormalities in coronary perfusion and severe myocardial metabolic disorder in patients with TTC based on the results of thallium-201 myocardial single-photon emission computed tomography (SPECT) and F-18 fluorodeoxyglucose (F-18 FDG) myocardial

positron emission tomography (PET). They noticed markedly decreased uptake of F-18 FDGon PET at the apical region while thallium 201 images showed only mildly reduced uptake. Reason for decreased uptake may be due to increased density of beta receptors noted in apex (53).Several studies have reported prolonged reduction and reduced uptake of F-18 FDG in patients subjected to multiple cycles of ischemia and reperfusion (54, 55). Still, the precise mechanism for reduced glucose uptake in stunned myocardium remains unknown.

LVOT obstruction & Myocarditis

According to earlier studies, LVOT obstruction is registered in 15-25% of patients with TTC (10, 56) and Kawaji et al detected it in 33% of patients (57). Although it was proposed as a possible pathophysiological mechanism of the disease, it remains uncertain whether it is a consequence rather than a cause of stress cardiomyopathy (37, 58).

Some researchers claim that there is much evidence indicating this relation actually exists. Transient dynamic LVOT gradient was detected at initial evaluation in a substantial proportion of patients described by Tsuchihashi et al. (1) and other investigators (24, 59). At least in some patients, a possible mechanism for TTC could be a dynamic LVOT obstruction preceding the ischemic event. Some of those patients, primarily women, may have geometric predisposition to dynamic LVOT obstruction, such as sigmoid or bulging interventricular septum (60, 61), reduced left ventricular volume (62-64) or abnormal mitro-aortic and septo-aortic angles (65), which may manifest only in the setting of intense adrenergic stimulation or hypovolemia (37). Elderly women have a higher tendency to develop hypertrophy of the basal anterior septum. The angle of the septum may cause increase in the speed in the outflow tract which simulate a hypertrophic cardiomyopathy (66). It is also associated with an abnormal orientation of the mitral valve due to flaccidity, deformity of valve, false chordae, disturbances of the papillary muscles, or systolic anterior movement (67-69) with mitral regurgitation. It is known that even in a normal heart, exposure to an exogenous catecholamine, such as dobutamine infusion, can precipitate dynamic LVOT obstruction (70).

If present, the dynamic obstruction increases apical LV wall stress and LV filling pressure, increasing myocardial oxygen demand at the mid-to-apical cavity. If this persists, apical hypoperfusion and ischemia may occur, with regional wall motion abnormality and stunning. Increased adrenergic tone might produce primary LVOT obstruction leading to secondary ischemia and focal wall-motion abnormalities. Physical or emotional stress could be the trigger of acute development of LVOT obstruction, which could produce severe apical ischemia. Identification of acute dynamic LVOT obstruction as the possible initial mechanism in some of the patients with stress cardiomyopathy may have important clinical and therapeutic implications (71).

Previously suggested possible role of a transient dynamic LVOT obstruction in the pathogenesis of this syndrome is not strongly supported by other investigators. According to Ishihara, it is unlikely that LVOT obstruction is the cause of TTC because most of these patients do not have LVOT obstruction. It is known that this condition is characterized not only by reduced apical LV wall motion, but also hyperkinesis of the basal LV wall, and that the combination possibly causes the LVOT obstruction (57, 72, 73). LVOT obstruction is not a prerequisite, but can contribute in a deteriorating clinical course of TTC (71, 73).

Takotsubo cardiomyopathy is characterized not only by reduced apical LV wall motion, but also hyperkinesis of the basal LV wall. This combination causes the LVOT obstruction in TTC.

The suggested possibility that myocarditis leads to transient LV dysfunction and Takotsubo cardiomyopathy is not well supported by the data. Arguments to rule out myocarditis include absence of typical clinical signs, unspecific findings on myocardial biopsy and negative results on serum tests for viral serology. Some studies used cardiac magnetic resonance

imaging, which has shown no evidence of myocarditis (35, 74-77).

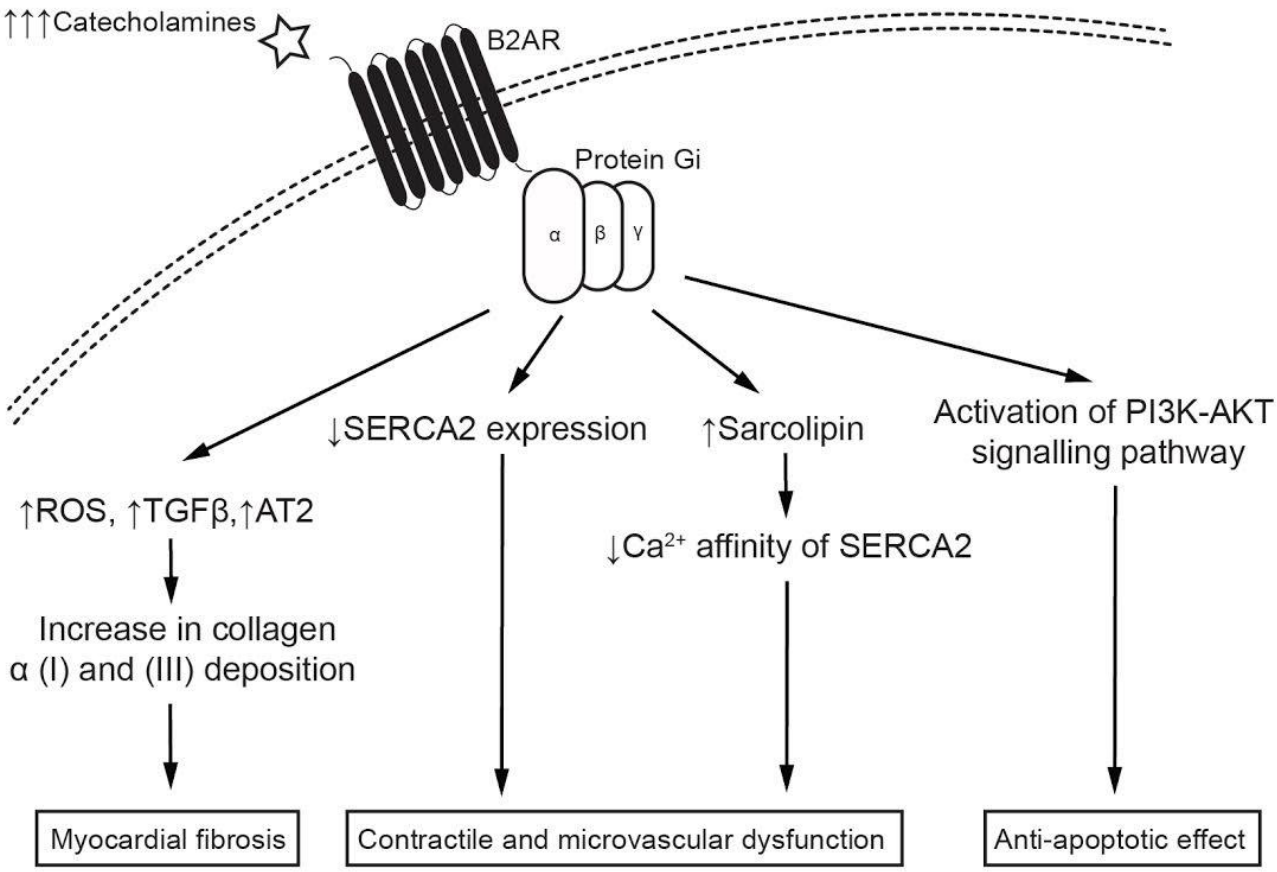
Catecholamines – pathophysiological hallmark of stress cardiomyopathy

Exposure to high intensity stress conditions, whether physical or emotional, has been associated with most cases of TTC (37). Furthermore, patients with pheochromocytoma, a catecholamine-producing tumor, are prone to develop a similar form of cardiomyopathy (78). In the animal model of subarachnoid hemorrhage, a condition with heightened catecholamine levels, a correlation between the extent of myocardial damage and sympathetic discharge was reported (79). Those observations suggest increased sympathetic activity and catecholamine mediated effect as a crucial factor for development of the broken heart syndrome. Although apart from catecholamine-mediated effect other theories about pathophysiology of stress cardiomyopathy coexist, the current Mayo Clinic criteria require catecholamine-producing tumor to be ruled out for establishing a TTC diagnosis (80).

Relationship between high levels of serum catecholamines and stress in patients suffering from cardiomyopathy was first shown in 2003 (76). Abraham et al. reported the emergence of all morphologic forms of TTC in patients exposed to catecholamines and other beta-receptor agonists used routinely during procedures and diagnostic tests (81). Study of Wittstein et al. reported that levels of catecholamines and dopamine are approximately two to three times higher in patients with TTC in comparison with cardiomyopathy caused by acute myocardial infarction (77). Interestingly, the correlation between morphological changes of the left ventricle in TTC and distribution of adrenoreceptors has been observed. A majority of β2 receptors with negative inotropic effect is in the apex of the left ventricle where ballooning process takes place which is consistent with a theory of catecholaminergic stress (39). Moreover, increased release of the catecholamines from the hearts of the patients affected with TTC has been reported (82). Some of the nuclear imaging studies also stressed the influence of the sympathetic nervous system in development of TTC. In eight patients with TTC, a decreased 123i-metaiodobenzylguanidine uptake within left ventricle was registered, indicating the existence of cardiac sympathetic hyperactivity as pathophysiological pathway (83). Moreover, a concordance between regional wall motion abnormalities and reduced uptake of the glucose and free fatty acid has been shown (84). Although this impairment of metabolism is not fully understood, catecholamine induced injury of cardiomyocytes is probably the cause of a metabolic stunned myocardium. Experiments in animals provided further evidence regarding the role of the catecholamines in disease patho-genesis. Iatrogenic administration of β2 agonists or immobilization stress in animals can result in reversible left ventricular apical ballooning. This adverse effect could be mitigated by α- and β-receptor blocking agents (85, 86).

Stress cardiomyopathy is characterized by similar molecular manifestations as the other catecholamine-mediated cardiomyopathies. Those morphological alterations caused by catecholamine overload include: extracellular matrix overproduction, contraction band necrosis and mononuclear cell infiltration (37). Catecholamine induced accumulation of collagen α-1 (I) chain in extracellular matrix results in large and rapid increase in fibrosis. High levels of catecholamine may result in high levels of profibrotic mediators (angiotensin II and free oxygen radicals), which can activate stimulating connective tissue growth factor, transforming growth factor β and the profibrotic osteopontin (87). Catecholamine overload stimulates β-adrenoreceptors and alters the expression of calcium-regulatory protein genes which cause alteration of the calcium regulatory system (88). Sarcolipin (SLN) and Phospholamban (PLN) are proteins of sarcoplasmic reticulum (SR) which regulate cardiac contractility. SLN regulates the sarcoplasmic/endoplasmic reticulum calcium ATPase 2 (SERCA2) by lowering its affinity for

Figure 1. *Schematic overview of pathophysiological mechanisms involved in catecholamine-mediated Takotsubo cardiomyopathy.*



calcium. In acute phase of TTC, ventricular expression of SLN is raised and could contribute to contractile dysfunction (89).

At physiological conditions, binding nore-pinephrine on β 1 – adrenoreceptors (β 1AR) and epinephrine on β 2 adrenoreceptors (β 2AR) in cardiomyocytes results in positive inotropic response. In normal human ventricular myocardium, there are four times more β 1AR than β 2AR (90). Positive inotropic response is the result of β 1AR or β 2AR activating stimulatory G protein (Gs) family, which activates protein kinase A (PKA) pathway reflected as an increased contractile response (91). Supraphysiological levels of catecholamines result in β 2-coupling from Gs to inhibitory G protein (Gi), which is reflected as a negative inotropic effect. This process is also called stimulus trafficking (92). The density of β 2AR is the highest in cardial apex, so there is the greatest negative inotropic effect (91). The β 2AR -Gi protein pathway can activate the p38 mitogen-activated protein kinase (MAPK) alteration of myofilament sensitivity. β 2AR–Gi protein has a favorable outcome on stress cardiomioypathy by stimulating the Pi3K–aKt-signaling pathway, which activates antiapoptotic genes (NF κ B1 and BCL2) (37). This is a physiological balance because β 1AR–Gs protein pathway has the proapoptotic effect (93). It is cardioprotective because it minimalizes catecholaminergic stimulation. After epinephrine levels are normalized, β 2AR–Gi switch to β 2AR–Gs or are degraded, which results in recovery of cardiomyocyte contractile function (91).

Although pathophysiological pathway of TTC is still unclear, it is certain that catecholamine overload presents a common denominator in development of the broken heart syndrome, as presented in Figure 1. Despite plentiful clinical findings, further research is obligatory to complete the puzzle of this rare but potentially severe disease.

Conclusion

Takotsubo cardiomyopathy is an important type of acute heart failure with transient left ventricular wall motion abnormalities. The symptomatology, echocardiographic and electrocardiographic features frequently mimic acute coronary syndrome, which is why TTC must be considered in a differential diagnosis of patients with acute chest pain. According to contemporary literature, TTC is most likely caused by supraphysiological levels of catecholamines due to acute mental stress. Elevated catecholamine levels induce myocardial fibrosis, and contractile and microvascular dysfunction. While the manifestation of TTC can be clinically dramatic and potentially life-threatening, the prognosis is usually excellent – 95% of patients fully recover within one to two months.

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