

**TAKOTSUBO CARDIOMYOPATHY - A REVIEW**Shivanjali Mallannagari<sup>1</sup>, Pravalika Ganagama<sup>2</sup>, Vyshnavi Pittala<sup>3</sup> and Kadarla Rohith Kumar\*

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**ABSTRACT**

Takotsubo cardiomyopathy (TCM) is a form of transient systolic dysfunction that masquerades myocardial infarction clinically. It is a reversible acute heart failure frequently precipitated by psychological or emotional or physical stress. The main focus of this review is providing comprehensive details of etiology, risk factors, epidemiology, clinical manifestations, diagnosis and consequences thereafter. The pathological data of this ballooning syndrome is inconsistent. The pathogenesis of this disorder is likely to be catecholamine mediated myocyte damage and micro vascular dysfunction; however, a number of possible alternative theories have been suggested. These include oxidative stress, transient coronary obstruction and estrogen deficiency.

**KEYWORDS:** Takotsubo cardiomyopathy; myocardial infarction; oxidative stress; transient coronary obstruction; estrogen deficiency.

**INTRODUCTION**

Left ventricular (LV) apical ballooning syndrome this syndrome resembles acute myocardial infarction in the absence of evident coronary artery occlusion.<sup>[1]</sup> Although the precise pathophysiology of takotsubo cardiomyopathy is still unknown, it seems that it is associated with excessive sympathetic stimulation, microvascular dysfunction, coronary artery vasospasm, and abnormal myocardial tissue metabolism.<sup>[2]</sup> The condition is known by many different names: stress-induced cardiomyopathy, broken heart syndrome and ampulla cardiomyopathy. The term takotsubo

cardiomyopathy is derived from the appearance of the mid-ventricle and apex of the heart on echocardiography or catheterization during systole; This apical ballooning resembles a spherical bottle with a narrow neck, not unlike the ancient Japanese octopus trap called takotsubo.<sup>[4]</sup> Left ventriculography during systole of patients with TCM demonstrates such a shape.<sup>[12]</sup> In most cases of stress cardiomyopathy, the regional wall motion abnormality extends beyond the territory perfused by a single epicardial coronary artery. The symptoms of broken heart syndrome are treatable, and the condition usually reverses itself in days or weeks.<sup>[4]</sup>

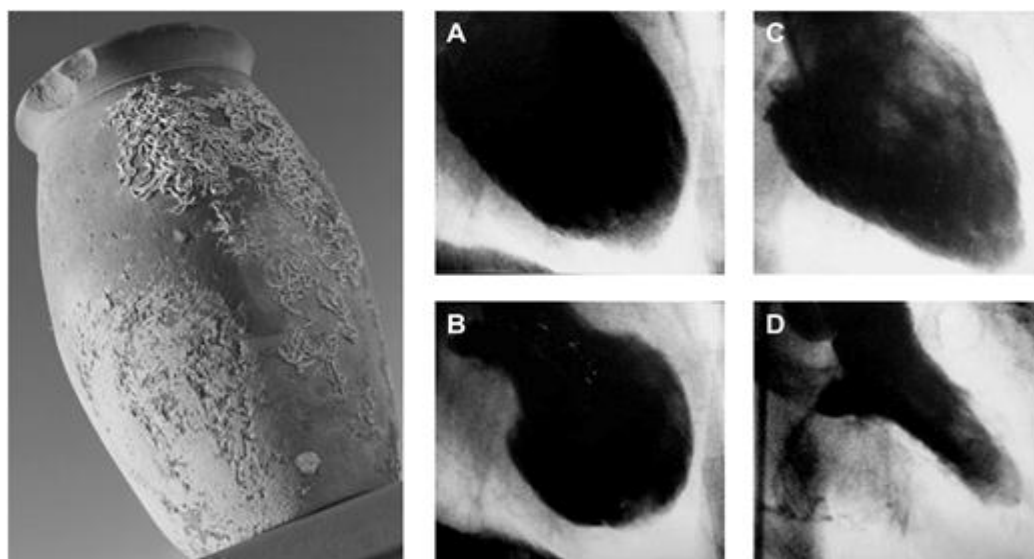


Figure 1: The appearance of the mid-ventricle and apex of the heart on echocardiography.<sup>[4]</sup>

## EPIDEMIOLOGY

The true prevalence of the apical ballooning syndrome remains uncertain.<sup>[1]</sup> It tends to affect women more than men, and is most common in women over 50 years of age (possibly after the menopause). According to a retrospective review, patients with TCM accounted for approximately 2% of all the patients with suspected acute coronary syndrome.<sup>[28]</sup> Further, 90% of these patients were postmenopausal women.<sup>[29]</sup> It is thought to affect around 2,500 people in the UK each year. It is not thought to be genetic, and so does not run in families (unlike some other types of cardiomyopathy).<sup>[7]</sup> Recent meta-analysis shows in-hospital mortality of 1–4.5% and recurrence rate of 5–10% during five year follow-up.<sup>[5]</sup> A review of the literature revealed 131 cases encountered in many different types of surgical procedures, with 37% occurring during anesthesia or surgery and 58% occurring postoperatively. Apical takotsubo cardiomyopathy was identified in 81.7% of patients, whereas the midventricular form was found in 14.6%, and basal and focal forms were diagnosed in 2.2% and 1.5%, respectively.<sup>[3]</sup>

SICM is diagnosed approximately in 1–2% of patients with history, signs and symptoms similar to acute myocardial infarction.<sup>[7]</sup> Most patients with SICM are postmenopausal women. A systematic review of 14 studies by Gianni *et al*<sup>[18]</sup> and Prasad *et al* showed 89% and 90% female predominance with age range of 58-77 and 58-75 years respectively. The reason of high prevalence in postmenopausal women is unknown but a hypothesis has proposed that reduced estrogens and their implications on microvascular system after menopause might be the main cause. Animal studies have shown estrogen attenuates immobility effects of stressors on the myocardium.<sup>[13]</sup>

## ETIOLOGY

### Physical Stressors

Physical stressors may be related to physical activities (for instance heavy gardening or sports), medical conditions, or procedures such as acute respiratory failure (e.g. asthma, end-stage chronic obstructive lung disease), pancreatitis, cholecystitis, pneumothorax, traumatic injury, sepsis, thyrotoxicosis, malignancy also including chemotherapy and radiotherapy, pregnancy, Caesarean section, lightning strike, near drowning, hypothermia, cocaine, alcohol or opiate withdrawal, and carbon-monoxide poisoning. Exogenous drugs in terms of catecholamines and sympathomimetic drugs may also act as triggers for TTS including dobutamine stress testing, electrophysiological testing (with isoproterenol or epinephrine) and beta-agonists for asthma or chronic obstructive lung disease. Also, acute coronary artery obstruction might act also as a trigger for TTS.

Nervous system conditions (e.g. stroke, head trauma, migraine intracerebral haemorrhage, or seizures) also represent an important trigger in the acute onset of TTS.<sup>[35]</sup>

## RISK FACTORS

### Lack of estrogen

More than 90% of patients with TCM are postmenopausal women. In fact, in a study to investigate if hormone replacement therapy had an effect on TCM, the authors concluded that none of the 31% patients with TCM received estrogen replacement therapy.<sup>[18]</sup> Moreover, Ueyama *et al*<sup>[17]</sup> demonstrated that the decrease in LV function was greater in ovariectomized rats subjected to restraint stress than in rats receiving estradiol supplementation. The myocytes are known to express estrogen receptor- $\alpha$  and estrogen receptor- $\beta$ . According to Ueyama *et al*<sup>[17]</sup>, estrogen enhanced transcription of cardioprotective factors such as heat shock protein and atrial natriuretic peptide, and in turn, protected against the toxic effects of catecholamines, calcium overload and reduced oxidative stress.<sup>[19]</sup>

### Emotional or physical stress inducers

A study reported on the prevalence of mood disorders and use of antidepressants in patients with TCM.<sup>[22]</sup> When patients with depressive disorders experienced a stressful event, vagus nerve tension was decreased and response to adrenal medullary hormone was increased, which may be relevant to the cause of the disease.<sup>[20]</sup> Further, some patients with depression showed very high noradrenaline extravasation.<sup>[21]</sup>

### Genetic factors

Certain polymorphisms of  $\alpha$ - and  $\beta$ -adrenergic receptors are associated with neurogenic stunned myocardium that occurs as symptom of subarachnoid hemorrhage and has overlapping pathophysiology with TCM.<sup>[23]</sup> Although adrenoceptor polymorphisms have not yet been identified in patients with TCM, patients with this disease showed L41Q polymorphism of G protein coupled receptor kinase (GRK5) more frequently compared with the control group.<sup>[24]</sup> L41Q polymorphism of GRK5 responds to catecholamine stimulation and attenuates the response of  $\beta$ -adrenergic receptors. Under catecholamine stimulation, balloon dilation of the ventricle may occur either by negative inotropic effect by  $\beta$ -receptor decoupling or ischemia because of an imbalance between  $\alpha$ 1-adrenergic coronary artery vasoconstriction and  $\beta$ -adrenergic vasodilation. These reports suggest the very interesting possibility that the susceptibility to TCM in individuals may be partially related to genetic factors.

It's also possible that some drugs, rarely, may cause broken heart syndrome by causing a surge of stress hormones. Drugs that may contribute to broken heart syndrome include:

- Epinephrine which is used to treat severe allergic reactions or a severe asthma attack.
- Duloxetine (Cymbalta), a medication given to treat nerve problems in people with diabetes, or as a treatment for depression.
- Venlafaxine (Effexor XR), which is a treatment for depression.

- Levothyroxine (Synthroid, Levoxyl), a drug given to people whose thyroid glands don't work properly<sup>[5]</sup>

patients are at risk for recurrence even years after the first event.

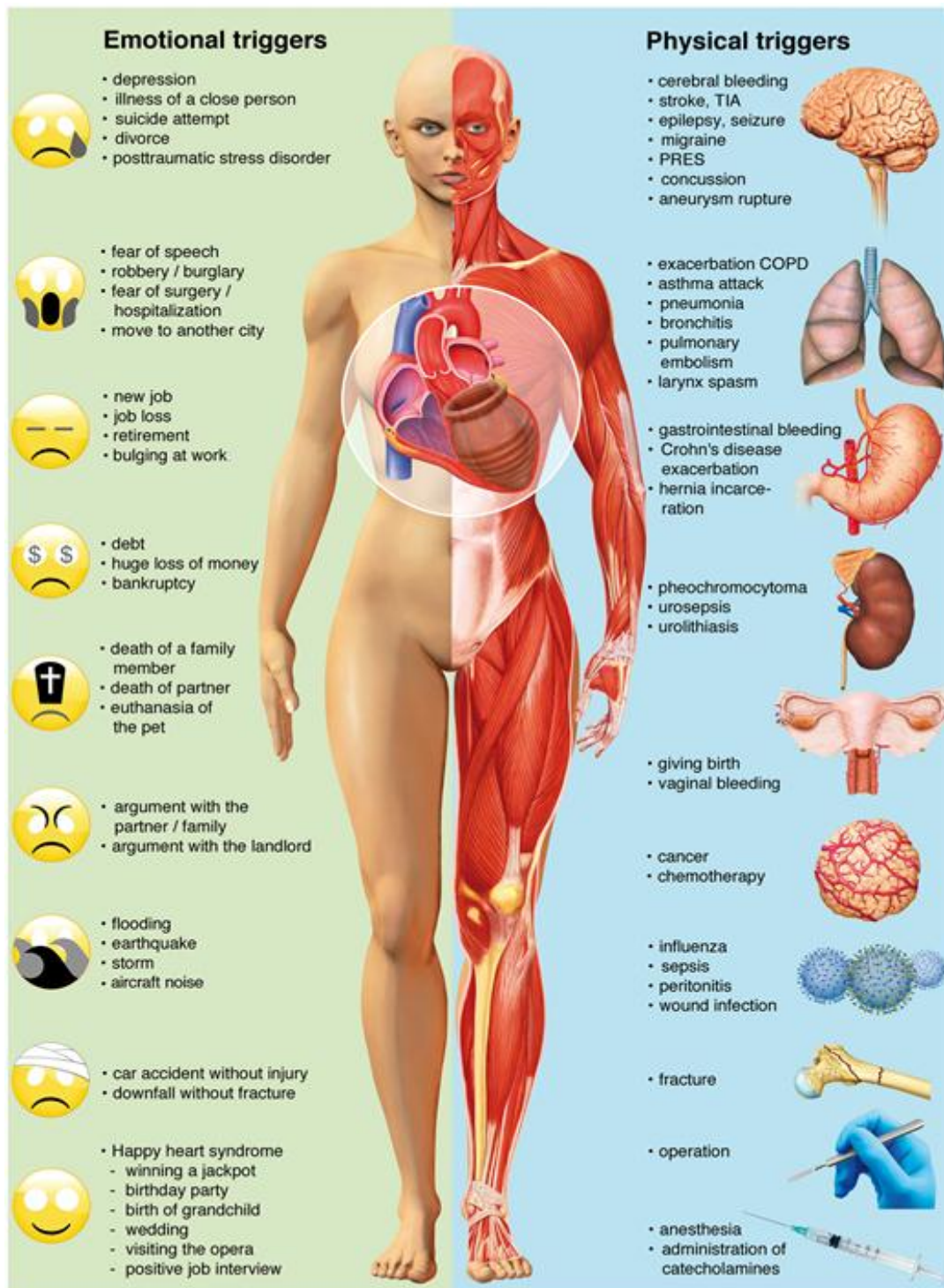


Figure 2: Triggering factors.

### Clinical Manifestations

The majority (88%) of patients with prior takotsubo cardiomyopathy had symptoms including fatigue (74%), shortness of breath (43%), palpitations (8%), and chest pain (8%). Most patients were New York Heart Association class I (70%), 10 patients were New York Heart Association class II (27%), and 1 patient was New

York Heart Association class III (3%). All control subjects were asymptomatic.<sup>[9]</sup>

### Complications

Hypotension and shock — Approximately 10 percent of patients with stress cardiomyopathy develop cardiogenic shock.<sup>[31]</sup> Factors associated with the development of

shock include younger age, lower LV ejection fraction (LVEF) and a physical triggers.<sup>[32]</sup> Backup of fluid into your lungs (pulmonary edema), Low blood pressure (hypotension), Disruptions in your heartbeat, Heart failure.<sup>[5]</sup>

**Table 1: Complications of stress cardiomyopathy.**<sup>[39]</sup>

Acute complications	Percentage
Right ventricular involvement	18–34%
Acute heart failure	12–45%
LV outflow tract obstruction	10–25%
Mitral regurgitation	14–25%
Cardiogenic shock	6–20%
Atrial fibrillation	5–15%
Ventricular arrhythmias	4–9%
Bradycardia, asystole	2–5%
Thrombus formation	2–8%
Pericardial tamponade	<1%
Ventricular wall rupture	<1%
In-hospital mortality	1–4.5%
Recurrence	5–22%
5-year mortality	3–17%

### Diagnosis

The following six are especially indicative of TCM: A. acute onset and stressful inducement: One of the unique features of TCM is its relation with stressful emotional or physical events. This characteristic was described in nearly two-thirds of the patients who developed TCM. Unlike acute coronary syndrome, with an onset peak early in the morning, TCM presents in the afternoon in most cases when stressful inducible events are likely to occur; B. electrocardiographic characteristics: Although the initial electrocardiogram (ECG) of patients with TCM is nonspecific, an ST segment elevation can be found mainly in the precordial leads in 50% of patients at onset. In addition, reciprocal ST-segment depression in the inferior wall leads is unlikely. In comparison with patients with base deformity, inverted T waves are more frequently observed in patients with apex balloon-like dilation and they resolve spontaneously within a few weeks to several months. Furthermore, patients with TCM usually present abnormal Q waves in precordial leads. These Q waves are transient in most patients and generally resolve within a few days to several weeks. C. cardiac enzymes: In most patients with TCM, there is slight elevation in the cardiac enzyme level on admission. The enzyme levels decrease rapidly and do not seem to have prognostic significance. D. Absence of coronary lesion: It is characteristic that no specific coronary lesions are detected in TCM. Generally, patients with TCM have chest pain, changes in ECG, elevation of cardiac enzyme levels, and wall motion abnormalities. Therefore, coronary angiography has to be conducted to rule out acute coronary syndrome; E. Balloon-like dilation of the ventricle: In contrast with acute myocardial infarction, LV wall motion abnormalities are found beyond a single coronary artery perfusion area in patients with TCM. Most patients with

TCM show loss of motion or hypokinesia at the apex and an apical balloon-like dilation pattern associated with preservation of the base. However, cases of a TCM subtype without abnormalities of the apex were reported recently. TCM is essentially characterized by LV failure, although, approximately, one-third of patients also have abnormalities in the right ventricle. Cardiac magnetic resonance imaging (MRI) is a suitable method to establish the diagnosis of TCM because this modality allows the accurate identification of reversible myocardium damage by visualization of wall motion abnormalities in each area, quantification of ventricular function, and assessment of inflammation and fibrosis. This modality brings new insight into the pathophysiology of TCM. It could enable early treatment of acute symptoms, raise awareness, and improve clinical outcomes. Cardiac MRI is appropriate to evaluate wall motion abnormalities and LV ejection fraction, and to confirm the absence of delayed gadolinium enhancement in patients with TCM. This allows differentiation of TCM from myocardial infarction and myocarditis, both pathologies associated with delayed gadolinium enhancement. Although coronary computed tomography angiography is not applicable to the first diagnosis of patients with TCM, there are many reports on its use for clinical course evaluation after TCM onset; F. Recovery of cardiac function: One of the characteristics of TCM is that thorough recovery of cardiac function is achieved.<sup>[12]</sup> the diagnosis of takotsubo cardiomyopathy appears to be unlikely in patients with troponin T greater than 6 ng/mL or troponin I greater than 15 ng/mL.<sup>[36]</sup>

### Differential Diagnosis: Comparison of Takotsubo Cardiomyopathy And Acute Coronary Syndrome

We compared a subgroup of 455 patients in whom takotsubo cardiomyopathy had been diagnosed with 455 age- and sex-matched patients with an acute coronary syndrome who either fulfilled the third universal definition of myocardial infarction<sup>14</sup> or had unstable angina caused by obstructive coronary artery disease. Data for patients with takotsubo cardiomyopathy were collected from five dedicated study centers (see the Methods section in the Supplementary Appendix), and data for patients with an acute coronary syndrome were collected from the Zurich Acute Coronary Syndrome Registry, since these centers had the most comprehensive patient records, including neurologic and psychiatric diagnoses according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition.<sup>[3]</sup>

### Diagnostic Criteria For Takotsubo Syndrome<sup>[38]</sup>

1. Transient hypokinesia or akinesia of LV with regional wall motion abnormality, majority involving apex & mid LV (or other areas) extending beyond the distribution of single epicardial artery; hypokinesia invariably (but not always) follows stressful trigger which could be emotional or physical.

2. Appearance of new ECG abnormalities like STelevation, T inversion, Q waves with mild elevation of troponins and pro-BNP markers.
3. Absence of obstructive lesion (plaque rupture, thrombus or spasm) of epicardial coronary artery (thus excluding STEMI, NSTEMI and Prinzmetal angina)
4. Absence of pheochromocytoma and myocarditis 4. Significant elevation of serum natriuretic peptide (BNP or NT-proBNP) during acute phase.
5. Positive but relatively small elevation of cardiac troponin measured with a conventional assay (troponin ve cases have been reported).
6. Absence of culprit atherosclerotic disease including plaque rupture, thrombus formation and coronary dissection or other pathological conditions to explain the pattern of temporary LV Dysfunction e.g. hypertrophic cardiomyopathy, viral myocarditis etc.
7. Recovery of ventricular function on cardiac imaging on follow up (3–6 months). (ECG-electrocardiogram, LV-left ventricle, BNP-brain natriuretic peptide, STEMI-ST elevation myocardial infarction, NSTEMI-NonST elevation myocardial infarction, RV-right ventricle, LBBB-left bundle branch block).

### Pathophysiology

Despite extensive research, the cause and pathogenesis of TTS remain incompletely understood. Stress cardiomyopathy represents a form of neurocardiogenic myocardial stunning, and while the link between the brain and the heart is established, the exact pathophysiological mechanisms remain unclear.<sup>[30]</sup>

It was initially characterized by a unique pattern of transient wall motion abnormality in the left ventricle characterized by apical ballooning and a hyperkinetic base occurring in the absence of significant epicardial coronary artery disease.<sup>[8]</sup>

### Catecholamine Toxicity

Catecholamines appear to have a central role in the pathophysiology of Takotsubo syndrome, as the trigger is often a sudden, unexpected stress; signs of sympathetic activation are present at presentation, and secondary medical triggers can also lead to extreme sympathetic activation. There are two initial elements of the physiology to consider. The first is the cognitive centres of the brain and hypothalamic–pituitary–adrenal (HPA) axis, and how much epinephrine and norepinephrine are released in response to a given stress (i.e. the ‘gain’ of the HPA axis). The second is the response of the cardiovascular system (including the myocardium, coronary arteries, and peripheral vasculature) and the sympathetic nervous system to the sudden sympathetic activation and surge in circulating catecholamines.<sup>[39]</sup>

Wittstein *et al*<sup>[26]</sup> found that the serum catecholamine concentration was two to three times greater in patients with TCM than that in patients with myocardial

infarction, and described that serious emotional stress is a precipitating factor. It has been reported that exogenously administered catecholamines and pheochromocytoma cause typical characteristics of TCM, which supports this theory further.<sup>[25]</sup>

Lyon *et al*<sup>[14]</sup> advocated a theory called “stimulus trafficking” that could explain the decline of myocyte contractile function in patients with TCM. Supraphysiological levels of catecholamines induce  $\beta_2$ -coupling from Gs to Gi. Therefore, the decline of myocyte contractile function is evidenced by hypokinesia in ECG. Involvement of the apex can be attributed to higher adrenoceptor density in the apex than in the base.<sup>[15]</sup> The rationale of stimulus trafficking is that a switch to Gi occurs to protect the myocytes from the strong stimulation of Gs, which causes apoptosis. Slow increases in serum troponin level explain early minimal necrosis of the myocardial tissue. Nef *et al*<sup>[16]</sup> showed increased activity of the phosphatidylinositol 3-kinase-protein kinase B (PI3K/AKT) signaling pathway, which has important anti-apoptosis functions and plays a role in the rapid recovery of myocytes. Thus, the transient LV dysfunction can be attributed to the PI3K/AKT pathway and inversely switching from Gi to Gs, associated with the homogeneous, prompt and clinically thorough recovery of systolic function observed in TCM.

### Sympathetic stimulation

The precise pathophysiological mechanisms of TTS are incompletely understood, but there is considerable evidence that sympathetic stimulation is central to its pathogenesis.<sup>[6]</sup> Analyses of heart rate variability have also demonstrated a sympathetic predominance and marked depression of parasympathetic activity during the acute phase.<sup>[34]</sup>

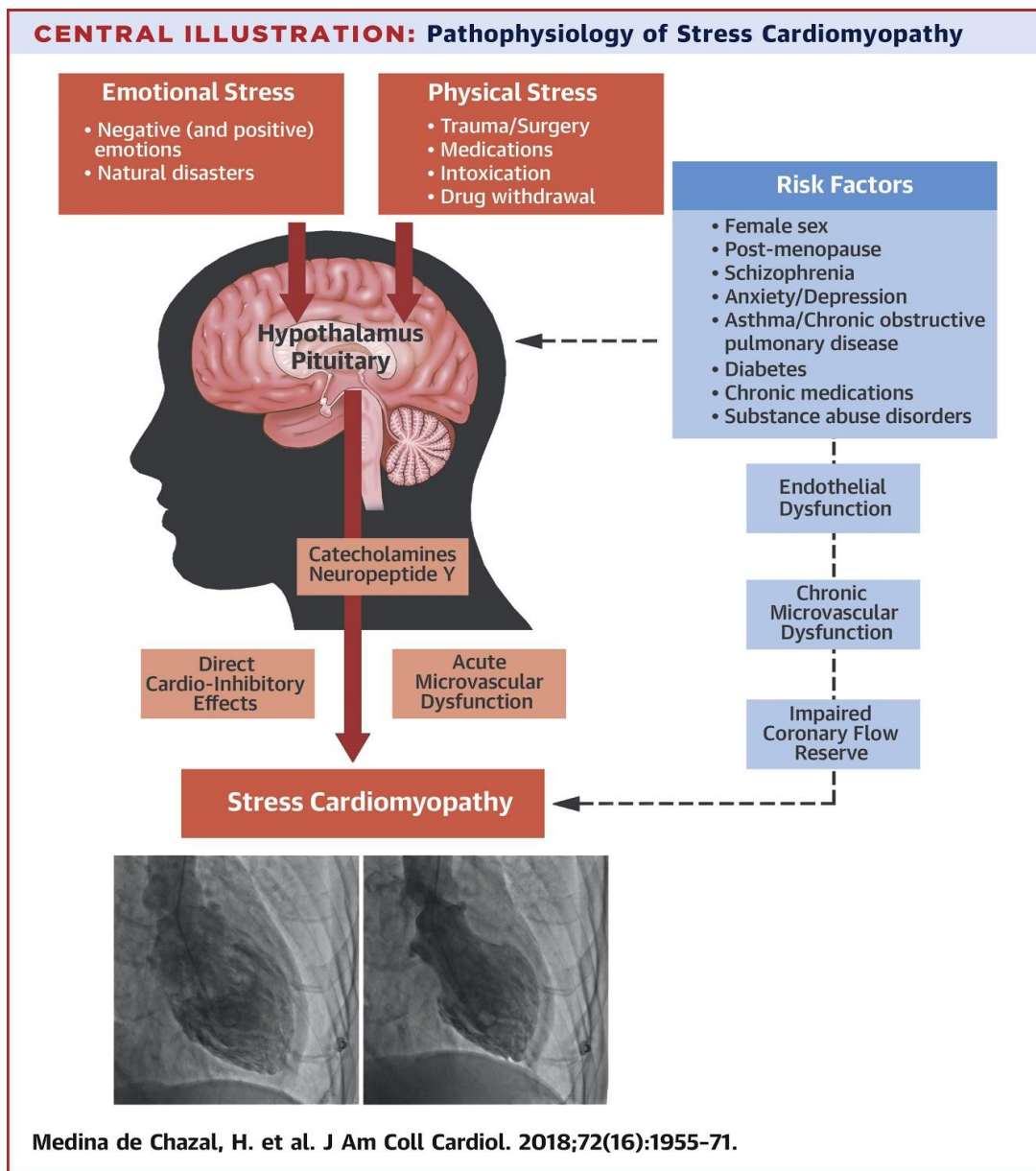


Figure 3: Pathophysiology of Stress Cardiomyopathy.<sup>[30]</sup>

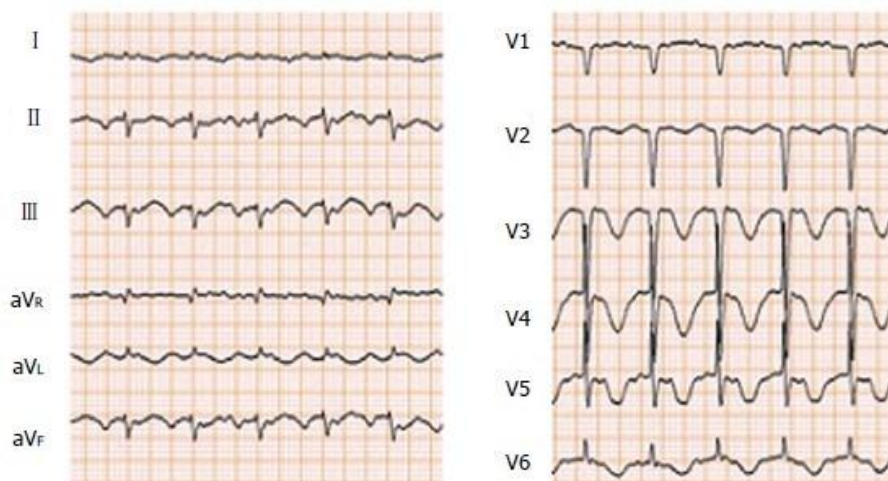


Figure 1: Inverted T waves are found in the limb and precordial leads, which is a common characteristic of takotsubo cardiomyopathy with apex balloon-like dilation.<sup>[27]</sup>

## TREATMENT

Stress cardiomyopathy is generally a transient disorder that is managed with supportive therapy. Conservative treatment and resolution of the physical or emotional stress usually result in rapid resolution of symptoms, although some patients develop acute complications such

as shock and acute heart failure (HF) that require intensive therapy. Appropriate management of shock varies depending upon whether significant left ventricular outflow tract (LVOT) obstruction is present.<sup>[33]</sup>

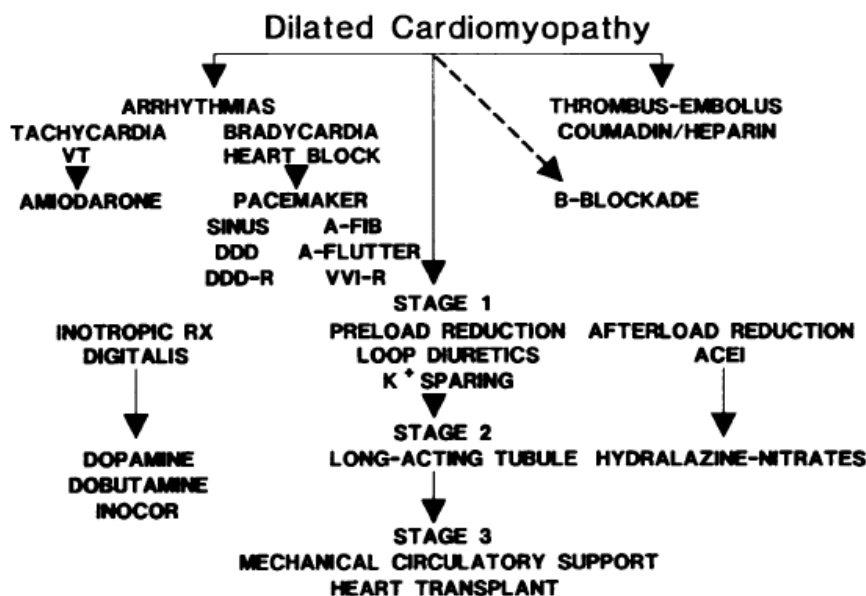


Figure 4: Dilated Cardiomyopathy Treatment.<sup>[43]</sup>

Medications commonly used to treat takotsubo cardiomyopathy include beta-blockers and angiotensin converting enzyme (ACE) inhibitor drugs. These drugs promote heart muscle recovery.

Anticoagulant drugs that interfere with blood clotting may be administered to avoid a stroke.

Complete recovery usually occurs within 1 to 3 months. Anti-anxiety or beta-blocker medication may be prescribed for a longer period of time to help control the release of stress hormones. It is also important to alleviate or manage the stress that may have played a role in triggering the disorder.<sup>[37]</sup>

Treatment of TCM during the acute phase is mainly symptomatic treatment. Intra-aortic balloon pump equipment is required for hemodynamically unstable patients in addition to cardiopulmonary circulatory support and continuous veno-venous hemofiltration.<sup>[40,41,42]</sup>

## DIURETICS

All patients with dilated cardiomyopathy and congestive heart failure retain sodium and water, which increases preload and causes pulmonary congestion and edema. Diuretics are an effective way to rapidly reduce volume overload and pulmonary congestion. The diuretic should increase urine output and reduce left ventricular filling pressure. Diuresis results in rapid symptomatic relief. We begin treatment with a loop diuretic and often add a potassium sparing, or distal tubule, agent. Because the

loop diuretics are short acting, patients in stage-2 failure may need an additional long-acting thiazide to achieve optimal effect.<sup>[44]</sup>

## AFTERLOAD REDUCTION

ACE Inhibitors. Angiotensin-converting enzyme (ACE) is responsible for the formation of angiotensin II from angiotensin I, and for the breakdown of bradykinin.<sup>3'</sup> ACE inhibitors dilate arteries constricted by angiotensin II, thereby lowering systemic vascular resistance; they also improve left ventricular function and cardiac output while decreasing preload and afterload, and favorably influence myocardial "remodeling."<sup>[44]</sup>

## IONOTROPIC AGENTS

Inotropic agents augment myocardial contractility. They appear to work in part by increasing intracellular calcium, which in turn reacts with contractile proteins to generate a greater force of myocardial contraction.  $\beta_1$ -agonist inotropic agents act by stimulating production of cyclic adenosine monophosphate (cAMP), which in turn facilitates calcium entry into the myofibrils. Phosphodiesterase inhibitors act by preventing the breakdown of cAMP. Inotropic agents produce a dose-responsive increase in cardiac output with improved renal flow and reduction of total body salt and water.

Despite their documented beneficial effect on myocardial contractility, chronic use of inotropic drugs remains controversial.

Dopamine. Dopamine exerts an inotropic effect on the myocardium through a direct action on  $\alpha_3$ , and dopamine receptors, or through the release of norepinephrine from terminal sympathetic neurons. The effect depends upon the dosage given. At low dosages (less than 2  $\mu\text{g}/\text{kg}/\text{min}$ ), dopamine activates dopaminergic receptors and increases renal flow while enhancing coronary artery and cerebrovascular dilation. At moderate dosages (2 to 5  $\text{mg}/\text{kg}/\text{min}$ ), dopamine activates,  $\alpha_1$ -adrenergic receptors and causes increased myocardial contractility with little change of heart rate, and with reduction or no change in systemic vascular resistance. High doses (5 to 10,  $\mu\text{g}/\text{kg}/\text{min}$ ) activate  $\alpha_1$ -adrenergic receptors and serotonin-sensitive receptors, and increase coronary and systemic arterial resistance and heart rate. In patients with severe heart failure, it is important not to give too much dopamine. Dopamine's strength lies in its ability, at proper doses, to restore cardiac output and increase sodium excretion.<sup>[44]</sup>

#### Management Considerations in Patients Presenting With Transient Stress-Related Cardiomyopathy

- Monitor in hospital on telemetry; observe for heart failure, arrhythmias, and mechanical complications
- Perform echocardiogram or magnetic resonance imaging to assess for LV function, mitral regurgitation, LV mural thrombus, right ventricular function, dynamic LV outflow tract obstruction, and other concomitant cardiac conditions
- Evaluate for dynamic obstruction in the LV outflow tract in those with a new systolic murmur, hypotension, and/or mitral regurgitation
- Anticoagulation with heparin to prevent LV mural thrombus formation in those with apical involvement if there are no contraindications to anticoagulation; consider oral anticoagulation with warfarin in those with significant persistent LV systolic dysfunction at the time of hospital discharge
- Standard medical therapy for LV systolic dysfunction including an adrenergic-blocking agent
- Repeat echocardiography before hospital discharge to reassess LV systolic function; consider repeating echocardiogram at 1 and 3 months in those with persistent LV dysfunction<sup>[10]</sup>

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