Epidemiology and pathophysiology of Takotsubo syndrome

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Abstract | Takotsubo syndrome is an acute cardiac syndrome first described in 1990 and characterized by transient left ventricular dysfunction affecting more than one coronary artery territory, often in a circumferential apical, mid-ventricular, or basal distribution. Several pathophysiological explanations have been proposed for this syndrome and its intriguing appearance, and awareness is growing that these explanations might not be mutually exclusive. The reversible apical myocardial dysfunction observed might result from more than one pathophysiological phenomenon. The pathophysiology of Takotsubo syndrome is complex and integrates neuroendocrine physiology, potentially involving the cognitive centres of the brain, and including the hypothalamic–pituitary–adrenal axis. Cardiovascular responses are caused by the sudden sympathetic activation and surge in concentrations of circulating catecholamines. The multiple morphological changes seen in the myocardium match those seen after catecholamine-induced cardiotoxicity. The acute prognosis and recurrence rate are now known to be worse than initially thought, and much still needs to be learned about the epidemiology and the underlying pathophysiology of this fascinating condition in order to improve diagnostic and treatment pathways.

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Introduction

During the past 25 years, a novel cardiac syndrome with transient left ventricular dysfunction has been reported all over the world. Often referred to as Takotsubo syndrome, owing to the shape and appearance of the left ventricle at end systole resembling a Japanese octopus fishing pot during the acute phase,[1] this disorder is also termed stress cardiomyopathy, apical ballooning, and, when triggered following bereavement, broken heart syndrome. Triggers of Takotsubo syndrome can be both psychological and physiological, and include illness, shock, and emotional stress. For example, many new cases were diagnosed after the earthquakes in Christchurch, New Zealand, in 2010 and 2011,[2] and in the USA in 2011 during Hurricane Irene, the worst tornado outbreak to hit the USA to date. Takotsubo syndrome is classified as both a primary and an acquired cardiomyopathy by the AHA,[3] and as an unclassified cardiomyopathy by the ESC.[4] Whether this disorder represents a true cardiomyopathy remains to be determined. In the meantime, we believe it should be considered clinically as an acute cardiac syndrome with reversible heart failure. In this Review, we discuss the epidemiology and the pathophysiological concepts of this novel cardiac syndrome.

Epidemiology

Although initially reported in Japan, Takotsubo syndrome has been observed worldwide. The largest reported cohort of affected patients comes from the Nationwide Inpatient Sample (NIS) in the USA, in which classification is based on discharge codes from the *International Statistical Classification of Diseases and Related Health Problems*.[5] In 2008, Deshmukh and colleagues analysed the NIS data from 6,837 patients with Takotsubo syndrome.[5] They confirmed the previously recurrent trend from smaller cohorts that the condition most frequently affects postmenopausal women—approximately 90% of patients with Takotsubo syndrome in the NIS cohort were aged ≥50 years and 90% were women. Additionally, 70% of patients were white, and only 1% of the overall cohort were Asian, confirming that this condition is not restricted to the Japanese population.[5]

Across multiple series, approximately 2% of all patients presenting to hospitals with suspected acute coronary syndromes have been identified as having Takotsubo syndrome,[6–8] the vast majority of whom were women aged ≥50 years.[9–12] If only women are considered, up to 10% of patients with suspected acute coronary syndromes are ultimately diagnosed as having Takotsubo syndrome.[5] The rate of Takotsubo syndrome among all patients in the initial NIS study ($n = 33,506,402$) was approximately 0.02%.[5]

Diagnosis

Diagnostic criteria for Takotsubo syndrome have been proposed from several centres (Box 1), using various diagnostic references.[6,13–16] A worldwide consensus has not yet been established. The evolution of diagnostic criteria reflects a change from a diagnosis of exclusion

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Competing interests
The authors declare no competing interests.

Key points

- Approximately 2% of patients who present to hospital with suspected acute coronary syndrome have Takotsubo syndrome, with a predominance in postmenopausal women
- Mortality is higher than initially thought, and recurrence is seen in 1.2% of patients within 6 months and nearly 5% at 6 years, with no preventive therapy currently available
- Systemic catecholamine surges can cause acute coronary and peripheral vasospasm followed by peripheral vasodilation; a common complication is cardiogenic shock, due at least in part to left ventricular systolic dysfunction
- Biopsy samples taken during the acute phase of Takotsubo syndrome show morphological changes similar to those after catecholamine-induced cardiotoxic effects, supporting direct effects as well as vascular influences
- The apical myocardium of the left ventricle has a high density of β-adrenoceptors and, therefore, is the region most sensitive to circulating catecholamines
- During extreme stress, excessive epinephrine levels cause a switch from the $G_s\alpha$ stimulatory to the cardioprotective $G_i\alpha$ cardioinhibitory secondary messenger pathway within cardiomyocytes, thereby acting as a positive inotrope

Box 1 | Diagnostic criteria for Takotsubo syndrome

Gothenberg (Sweden)[14]

Transient hypokinesis, akinesis, or dyskinesis in segments of the left ventricle, and frequently a stressful trigger (psychological or physical)

- Absence of other pathological conditions (for example, ischaemia, myocarditis, toxic damage, and tachycardia) that might more credibly explain the regional dysfunction
- Slight or no increase in cardiac troponin levels (disparate with the amount of myocardial dysfunction)

Italina network (Italy)[16]

Typical transient LV wall-motion abnormalities extending beyond one epicardial vascular distribution, with complete functional normalization within 6 weeks

- Absence of potentially culprit coronary stenosis or angiographic evidence of acute plaque rupture, dissection, thrombosis, or spasm
- New and dynamic ST-segment abnormalities or T-wave inversion
- Onset of transient or permanent left-bundle-branch block
- Mild increase in myocardial injury markers (creatine kinase MB <50 U/L)
- Clinical and/or instrumental exclusion of myocarditis
- Postmenopausal woman (optional)
- Antecedent stressful event (optional)

Mayo Clinic (USA)[6]

Transient akinesis or dyskinesis of LV wall-motion abnormalities (ballooning) with chest pain

- Electrocardiographic changes (ST-segment elevation or T-wave inversion)
- No substantial obstructive epicardial coronary artery disease
- Absence of pheochromocytoma or myocarditis

MRI-based (USA and Europe)[15]

- An acute cardiac event typically presenting with chest pain and/or dyspnoea
- Transient systolic dysfunction with marked LV contraction abnormality (akinesia or dyskinesia of the LV apical and/or midventricular or basal segments)
- Absence of severe (>50%) obstructive coronary artery disease or angiographic evidence of acute plaque rupture
- Electrocardiographic abnormalities (ST-segment elevation or T-wave inversion)
- Slightly raised cardiac troponin level
- Absence of pheochromocytoma
- Absence of myocarditis or typical ischaemic transmural late gadolinium enhancement on cardiovascular MRI (if available)

(apical bulge with no coronary disease) to a recognition that Takotsubo syndrome has characteristic features, such as catecholamine-stimulated myocardial stunning and evidence of inflammation on acute imaging. Myocardial oedema in affected segments can be visualized on T2-weighted short-tau inversion recovery MRI. The possibility that Takotsubo syndrome and bystander coronary disease could coexist is also important to remember, as not all patients with Takotsubo syndrome have normal coronary arteries.

Emotional and/or physical stress frequently, but not always, precedes the onset of Takotsubo syndrome (Box 2).[17] Stressors are often common events encountered in daily life. A variety of noncardiac acute diseases, drugs, and symptoms might also trigger Takotsubo syndrome (Box 2). Differentiation of Takotsubo syndrome from acute coronary syndromes can be challenging because many of the symptoms, clinical signs, and echocardiographic and electrocardiographic findings are superficially similar, such as cardiac chest pain, ST-segment elevation, and regional wall-motion abnormalities.[18–23] Takotsubo syndrome is generally diagnosed when coronary angiography shows no coronary stenosis and the regional wall-motion abnormalities extend beyond a single coronary artery territory. Urgent invasive diagnostic coronary angiography is mandatory in patients who present with acute chest pain and ST-segment elevation. However, if presentation is delayed (for example, >48 h) or patients are pain free and stable at presentation, CT coronary angiography could be useful as an alternative imaging investigation to exclude coronary stenosis.[24]

Electrocardiographic abnormalities such as ST-segment elevation in the acute phase and subsequent deep and widespread T-wave inversion, are often present in patients with Takotsubo syndrome.[18–23,25,26] These changes evolve over time from symptom onset, however, and distinction from ST-segment-elevation myocardial infarction (STEMI) soon after onset can be challenging. Thus, access to emergency coronary angiography should not be delayed.[18–23] Although electrocardiogram-based diagnostic criteria have been suggested to differentiate Takotsubo syndrome from acute myocardial infarction (MI), no set of criteria has yet proven sufficiently sensitive and specific. Kosuge *et al.*[19] reported differences in the distribution of ST-segment elevation between patients with Takotsubo syndrome and those with STEMI. Most patients with anterior acute MI had ST-segment elevation in leads V2–V4. By contrast, in patients with Takotsubo syndrome, ST-segment elevation most frequently occurred in leads II, III, aVF, aVR, and V5–6 facing the apical and inferolateral regions. The wall-motion abnormalities in Takotsubo syndrome occasionally extend to the V1-lead regions. This method potentially has ≥90% sensitivity and specificity in distinguishing between Takotsubo syndrome and acute anterior MI, but has not been tested prospectively and, therefore, should not be applied to withhold STEMI-guideline-based therapy at acute presentation.[19]

As well as the classic apical variant of Takotsubo syndrome, other forms have been described, including the midventricular and the basal or inverted variants.[7,11,12,28,29] No evidence suggests that electrocardiography can accurately distinguish between anatomical variants. The reported incidence of nonapical variants overall ranges from 8.4% to 40.0%,[7,11,29] with the prevalence of

the mid-ventricular type at least 20%, and the basal type approximately 3%.

As suggested by the high number of women aged ≥50 years in the NIS cohort, oestrogen concentration is thought to contribute to syndrome onset, although this hypothesis is currently only supported by data derived from preclinical models.[30] A study using rats suggested that chronic oestrogen supplementation could at least partially attenuate the excessive cardiovascular response to stress,[31] but this has not been performed in a clinical trial. Additionally, this oestrogen theory does not explain the occurrence of Takotsubo syndrome in men. Further studies are required to clarify the reasons underlying the striking difference between the sexes.

Prognosis

Mortality

The prognosis of Takotsubo syndrome was initially reported to be favourable compared with that for STEMI,[32] but subsequent studies demonstrated that acute[5] and long-term[33,34] mortality are both higher than previously recognized. The prevalence of prehospital mortality is unknown, but should not be underestimated, as mortality during the acute phase in hospitalized patients is 4–5%, which is similar to the mortality seen in patients with STEMI. Furthermore, despite the recovery of left ventricular function and absence of stenotic coronary artery disease, mortality after hospital discharge is notably higher than that in aged-matched healthy populations.[33] The prognosis is greatly influenced by non-cardiac diseases,[35] as many patients experience Takotsubo syndrome secondary to other diseases.[10] Among a cohort of patients with Takotsubo syndrome in Italy, in-hospital complications were experienced by approximately 50% of patients aged ≥75 years, compared with 25% of patients aged <75 years.[36] These trends were also noted in the German Takotsubo registry.[37] In the largest published cohorts, the in-hospital mortality was 2.2% in Germany and Austria,[38] 2.6% in Italy,[39] 4.2% in the USA,[40] 6.8% in Japan,[12] and 4.5% in a meta-analysis of these studies.[41]

Japanese investigators have reported that Takotsubo syndrome that is triggered in hospital secondary to an existing illness (such as malignancy, chronic diseases, acute diseases, and infectious diseases) is associated with significantly higher in-hospital mortality compared with onset outside hospital (odds ratio 2.02, 95% CI 1.43–2.85).[12] The mortality in men seems to have been higher than that in women in several reports, but patient numbers were low. Cardiogenic shock, cardiac arrest,[42] and mortality,[43–45] are more frequently seen in men than women. The presence of a J wave on the electrocardiogram in the acute phase is a potential marker of increased risk of ventricular tachyarrhythmia and sudden cardiac death.[46] Although the mechanical complications in Takotsubo syndrome are not fully understood, they are clinically serious and the risk of death is high. Identification of clinical features predictive of mechanical complications and understanding the mechanisms underpinning them will aid improvement of clinical treatment pathways.

Box 2 | Potential stressors for Takotsubo syndrome

Emotional stress

- Anger
- Accident
- Death, severe illness, or injury of a family member, friend, or pet
- Natural event (for example, an earthquake)
- Financial loss (through business or gambling)
- Involvement with legal proceedings
- Move to a new residence
- Panic
- Public speaking
- Receiving bad news
- Severe argument
- Surprise party

Physical stress

- Anaemia due to gastrointestinal bleeding
- Cocaine use
- Drug reaction
- Electroconvulsive therapy
- Excessive insulin administration
- Noncardiac surgery or procedure (such as a cholecystectomy, hysterectomy, or nosebleed treated with phenylephrine)
- Recovery from general anaesthesia
- Severe illness (such as asthma or acute exacerbation of chronic obstructive pulmonary disease, connective tissue disorders, acute cholecystitis, encephalitis, fracture, subarachnoid haemorrhage, pseudomembranous colitis, cancer, endocrine neoplasia, and thyrotoxicosis)
- Severe pain (such as fracture, renal colic, pneumothorax, and pulmonary embolism)
- Stress test, such as dobutamine stress echocardiogram or exercise*
- Suicide attempt*
- Withdrawal from alcohol or opiates*

*Potentially a trigger of both emotional and physical stress. Adapted and reproduced with permission from Annual Reviews © Akashi, Y. J., Nef, H. M., Möllmann, H. & Ueyama, T. Stress cardiomyopathy. *Annu. Rev. Med*. **61**, 271–286 (2010), and Elsevier © Prasad, A., Lerman, A. & Rihal, C. S. Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction. *Am. Heart J.* **155**, 408–417 (2008).

Recurrence

The reported average recurrence rate of Takotsubo syndrome has ranged from 0 to 22%, dependent on the size of the series studied and duration of follow-up (Table 1). Singh and colleagues[47] reported that the annualized recurrence rate was about 1.5% and the cumulative incidence of recurrence increased from 1.2% at 6 months to nearly 5% at 6 years. For recurrence, the predominance in women is maintained. In patients aged <50 years, the median recurrence rate was higher than in those aged ≥50 years.[10] This difference might reflect a greater proportion of younger patients having secondary Takotsubo syndrome, where the triggering event is more likely to recur. No evidence supports any specific treatment to prevent recurrence; a meta-analysis showed a lack of efficacy with all therapies assessed.[48] Recurrence has been reported in the context of β-blockers, which are perhaps the most logical pharmacological preventive strategy, given the stressful trigger and potential role of catecholamines.[48]

Table 1 | Recurrence rates of Takotsubo syndrome

Authors	Country	Year reported	Recurrence cases/all patients	Recurrence rate (%)
Tsuchihashi *et al.*[65]	Japan	2001	2/72	2.8
Desmet *et al.*[94]	Belgium	2003	1/13	7.7
Bybee *et al.*[95]	USA	2004	1/16	6.2
Akashi *et al.*[96]	Japan	2005	0/13	0
Sharkey *et al.*[97]	USA	2005	1/11	9.1
Gianni *et al.*[98]	Italy and Canada	2006	6/169	3.5
Hertting *et al.*[99]	Germany	2006	0/32	0
Kurowski *et al.*[7]	Germany	2007	2/35	5.7
Elesber *et al.*[32]	USA	2007	10/100	11.4
Spedicato *et al.*[100]	Italy	2008	2/29	6.9
El Mahmound *et al.*[101]	France	2008	0/32	0
Previtali *et al.*[102]	Italy	2009	1/18	5.6
Eshtehardi *et al.*[103]	Switzerland	2009	2/41	4.9
Regnante *et al.*[104]	USA	2009	2/70	2.9
Teh *et al.*[105]	Australia	2010	0/23	0
Primetshofer *et al.*[9]	Austria	2010	1/31	3.2
Sharkey *et al.*[33]	USA	2010	7/136	5.1
Song *et al.*[35]	Korea	2010	0/87	0
Parodi *et al.*[106]	Italy	2011	2/116	1.7
Nunez-Gil *et al.*[107]	Spain	2012	4/100	4.0
Brenner *et al.*[108]	Switzerland	2012	2/17	11.7
Samardhi *et al.*[109]	Australia	2012	0/51	0
Bellandi *et al.*[110]	Italy	2012	0/105	0
Cacciotti *et al.*[111]	Italy	2012	1/75	1.3
Vriz *et al.*[43]	Italy	2013	5/23	21.7
Sharma *et al.*[112]	UK	2013	0/12	0
Pullara *et al.*[113]	Italy	2013	2/26	7.7
Patel *et al.*[10]	USA	2013	7/224	3.1
Showkathali *et al.*[114]	UK	2014	0/17	0
Murakami *et al.*[11]	Japan	2014	9/107	4.7
Nishida *et al.*[29]	Japan	2014	7/251	2.8
All	—	—	77/2052	3.8

Adapted and reproduced with permission from Elsevier © Singh, K. *et al.* Systematic review and meta-analysis of incidence and correlates of recurrence of takotsubo cardiomyopathy. *Int. J. Cardiol.* **174,** 696–701 (2014).

Pathophysiology

Evidence from clinical studies supports the hypothesis of excess catecholamine concentration as a trigger of Takotsubo syndrome.[49] The temporal relationship between a stressful psychological event and the rapid onset of clinical symptoms and the number of cases triggered by iatrogenic catecholamine administration suggest a strong link. More-extensive investigation of human biopsy samples taken during the acute phase and after functional recovery, however, is required. Therefore, we discuss here the histological insights available and other descriptive results that we believe further the understanding of this cardiac entity.

Clinical histological studies

Histological studies of myocardial biopsy samples taken during the acute phase of Takotsubo syndrome and at follow-up have shown characteristic morphological changes that are similar to the cardiotoxic effects induced by catecholamines (Figure 1).[49] Electron microscopy of the myocardium shows damage to contractile proteins, with numerous vacuoles of different sizes and with varied contents (myelin bodies and residual cellular products) and enlarged diameter of myocytes (representative of myocyte hypertrophy).[49] Areas of nonspecified cytoplasm and clusters of mitochondria with abnormal size and shape have been observed. Contraction bands consistent with cytoplasmic calcium overload and fixed myofilament crossbridging have also been found sporadically. Cardiomyocyte nuclei are abnormal in appearance, with altered size and location, typically at the cell border.[49] Cell swelling is associated with damage of the basal lamina, but no signs of necrosis and oncotic cell death associated with ischaemic injury have been detected. The acute catecholamine-like-induced changes in myocardial composition and appearance and disarrangement of the cytoskeletal and contractile proteins are restored to normal after functional recovery.[49] Typical structural changes as a result of catecholamine overload also include reversible intracellular arrangements (α-actinin, actin, titin) and mild neutrophilic infiltration. The presence of myofibroblasts in the very early stage of Takotsubo syndrome might play a protective role by minimizing myocardial disarray.[49]

The extracellular matrix is enlarged in the acute phase of Takotsubo syndrome and stains positively for collagen type I.[48] This rapid alteration is mainly triggered by an increased ratio of collagen α-1 (I) chain to collagen α-1 (III) chain expression and deposition. Fibronectin staining has confirmed increased fibrosis and an association between high norepinephrine or epinephrine levels and high levels of profibrotic mediators, such as angiotensin II and free radicals, has been suggested. These and other factors lead to the activation of transforming growth factor-β, which stimulates secretion of connective tissue growth factors and the profibrotic osteopontin.[50] The degree of fibrosis, however, does not become critical and, therefore, structural integrity is maintained.

One of the most striking histological observations in patients with Takotsubo syndrome is the rapid regression of fibrosis.[50] Expression and proteolytic activity of matrix metalloproteinase (MMP)-9 is substantially upregulated during the acute phase of Takotsubo syndrome. Proteolytic activity of MMPs, which is regulated by endogenous physiological inhibitors, leads to the degradation of several components of the extracellular matrix. Therefore, the balance between MMPs, tissue inhibitors of MMPs (TIMP), and their regulators determines the progression of myocardial fibrosis.[50] Accordingly, the significant reduction of TIMP-3 mRNA and protein concentrations during the recovery phase of Takotsubo syndrome causes disinhibition of MMP activity and leads to increased degradation of the extracellular matrix.[50]

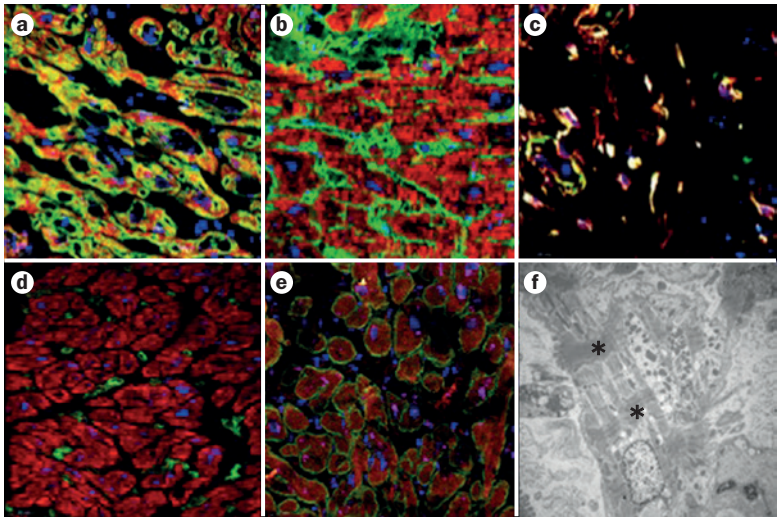

Figure 1 | Histopathological features of Takotsubo syndrome. **a** | Immunohistochemistry of intracellular proteins shows α-actinin (specific labelling green, phalloidin red, nuclei blue) only in the border zone.[49] **b** | The extracellular matrix shows increased concentrations of collagen type I and the myocardial syncytium is separated.[49] **c** | Myofibroblasts are present, which confirms the hypothesis of a catecholamine-triggered depression of left ventricular function. **d** | Capillary density is reduced (stained by CD31, green).[50] **e** | Sarcolipin, shown in red, is present in the left ventricle during the acute phase of Takotsubo syndrome, and contributes to disturbed regulation of calcium homeostasis.[91] **f** | The myocardium contains numerous vacuoles of varying size and contents (myelin bodies and residual cellular products), loss of contractile material, and areas of nonspecified cytoplasm. The asterisk indicates interstitial space widened owing to formation of cellular debris and contraction bands of sarcomeres.[49] Permission for Figure 1a, b, and f obtained from Oxford University Press © Nef, H. M. *et al.* Tako-tsubo cardiomyopathy: intraindividual structural analysis in the acute phase and after functional recovery. *Eur. Heart J.* **28**, 2456–2464 (2007). Permission for Figure 1d obtained from Elsevier © Szardien, S. *et al.* Molecular basis of disturbed extracellular matrix homeostasis in stress cardiomyopathy. *Int. J. Cardio.* **168,** 1685–1688 (2013). Permission for Figure 1e obtained from Oxford University Press © Nef, H. M. *et al.* Abnormalities in intracellular Ca^{2+} regulation contribute to the pathomechanism of Tako-Tsubo cardiomyopathy. *Eur. Heart J.* **30**, 2155–2164 (2009).

Molecular studies have demonstrated activation of the phosphoinositide-3-kinase (PI3K)/AKT signalling pathway in Takotsubo syndrome, which might contribute to a favourable outcome by promoting cell survival and increasing protein biosynthesis. These two factors are essential for myocardial regeneration and improvement of left ventricular function.[51] In the acute phase of Takotsubo syndrome, immunohistochemical staining for macrophages (CD68) revealed the presence of several extracellular clusters.[49] Slightly increased leukocyte counts and C-reactive protein levels are widely reported.[49] The main pathological features of the autopsied hearts from patients with Takotsubo syndrome are myocardial injury and its sequelae resembling those found after catecholamine-induced myocardial injury.

Additional documented features are marked elevation of natriuretic peptide levels at presentation in such patients. N terminal pro-B-type natriuretic peptides (BNP) and BNP levels increase with increasing catecholamine concentrations and correlate with the severity of left ventricular systolic dysfunction. BNP concentrations in Takotsubo syndrome are substantially higher than those in acute MI. Early ratios of BNP to troponin T and of BNP to creatine kinase MB might help to differentiate Takotsubo syndrome from acute MI with greater accuracy than measurement of BNP alone.[52]

Alterations in calcium-regulated protein

The stimulation of β-adrenoceptors by supraphysiological levels of catecholamines leads to alterations in calcium-regulated protein concentrations in patients with Takotsubo syndrome. The homologous intrinsic membrane proteins sarcolipin and phospholamban, which are confined to the sarcoplasmic reticulum, are critical regulators of cardiac contractility.[53] Unusually high ventricular expression of *SLN* and concentrations of sarcolipin have been noted in the acute phase of Takotsubo syndrome (Figure 1).[54] Sarcolipin negatively regulates sarcoplasmic/endoplasmic reticulum calcium ATPase (SERCA2) concentrations by lowering its affinity for calcium. After functional recovery, regression of gene expression and protein concentration has been reported.[54] These findings suggest a calcium-dependent depression of contractile function in Takotsubo syndrome.

Phospholamban, another important regulator of SERCA2 activity, is also substantially upregulated during the acute phase of Takotsubo syndrome.[55] Sarcolipin is located in the same sarcoplasmic reticulum membrane subcompartments as phospholamban, which leads to a superinhibitory effect on the SERCA2 pump. Perhaps paradoxically, in the aftermath of intense β-adrenoceptor activation, the cAMP-dependent protein kinase (PKA) Cα-dependent and calcium/calmodulin-dependent kinase (CaMK) II subunit γ-dependent phosphorylation pathways are altered, which leads to dephosphorylation, particularly of phospholamban Ser16 and Thr17, and further increases the inhibitory effect on SERCA2a.[55] Immunohistochemistry studies showed that the fluorescence intensity of phospholamban Ser16 was lower in biopsy samples taken during the acute phase of Takotsubo syndrome than in healthy myocardium. Although there is no direct evidence that the reported alterations in the expression of calcium-regulatory proteins lead to the acute detrimental effects of Takotsubo syndrome, evidence suggests that intense G-protein-stimulated β1-adrenoceptor signalling can directly modulate gene expression via the CAMP responsive element binding protein 1 (CREB-1) and nuclear factor of activated T-cells (NFAT) signalling pathways.[56]

Stress-hormone-induced disturbances

Increased extracellular fibrosis is generally associated with disturbed microcirculation. In Takotsubo syndrome, endomyocardial capillary density is substantially reduced, mainly due to the expansion of the extracellular matrix.[49,50] Ultimately, these changes result in a mismatch between oxygen supply and demand in cardiomyocytes. Ultrastructural analysis of myocardial tissue has clearly shown intracellular vacuoles and accumulation of ubiquitin in the myocardial samples taken during the acute phase of Takotsubo syndrome.[49]

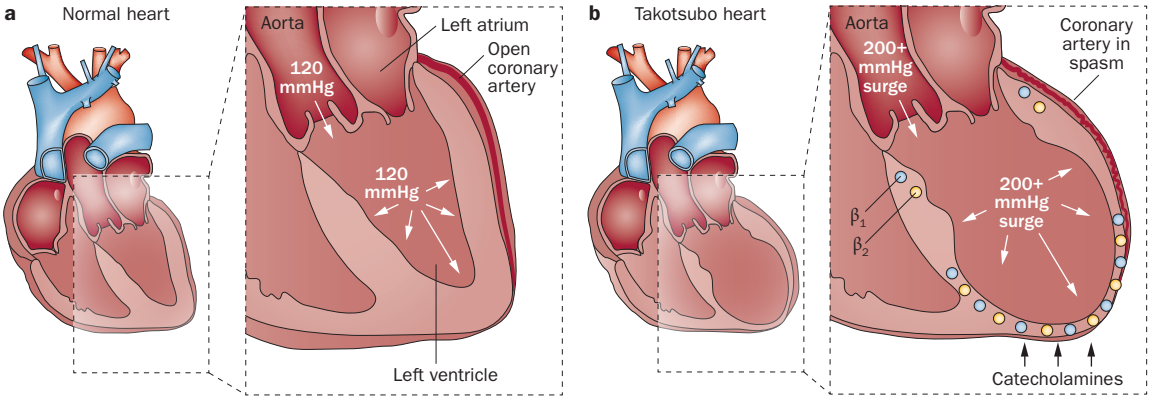

Figure 2 | Integrated pathophysiological model for acute apical dysfunction in Takotsubo syndrome. **a** | Left ventricular systolic performance under normal conditions of perfusion, afterload, and β-adrenoceptor activation. **b** | The acute phase of Takotsubo syndrome can be characterized by peripheral arterial vasospasm leading to increased afterload and transient high left ventricular end-systolic pressure, acute coronary artery vasospasm causing myocardial ischaemia, and a subsequent reduction in cardiac output with systemic hypotension and direct catecholamine-mediated myocardial stunning in the apex where the β-adrenoceptor gradient is highest.

These results indicate a potential oxygen deficiency that contributes to cardiomyocyte dysfunction.

The central role of catecholamines

The pathophysiology of Takotsubo syndrome is complex and reflects the integrated cardiovascular responses to sudden surges in endogenous catecholamine concentrations or to exogenously administered catecholamines, often in the context of acute severe stress. Several clinical conditions, including acute subarachnoid haemorrhage, phaeochromocytoma, and acute thyrotoxicosis, are associated with acute severe sympathetic neural activation or adrenal catecholamine release that can trigger Takotsubo syndrome.[57] Many observational clinical studies and some laboratory models have helped to provide evidence that forms the basis for several pathophysiological hypotheses. The role of catecholamines seems to be central to the pathophysiology of Takotsubo syndrome, and leads to multiple potentially relevant direct and indirect effects on the brain, systemic vasculature, coronary vasculature, and myocardium.[57]

The pathophysiology of Takotsubo syndrome can be broadly considered in two phases. The first starts with increased release of epinephrine and norepinephrine, initiated by the cognitive centres of the brain through activation of the hypothalamic–pituitary–adrenal (HPA) axis in response to a given stress, which is termed HPA gain. Catecholamine concentrations in serum are substantially elevated at presentation with Takotsubo syndrome compared with resting levels in the same patients and those in comparable patients with acute heart failure secondary to acute MI. These differences suggest the potential for excessive HPA gain and epinephrine release in susceptible individuals.[58] This effect is most relevant for Takotsubo syndrome cases triggered by emotional stress. The thresholds for stress tolerance and HPA gain are incompletely understood. The incidence of stress and anxiety disorder is higher in cohorts with Takotsubo syndrome than in control emergency populations,[5] although stress and anxiety might only serve to increase susceptibility, rather than be the isolated cause. Resting catecholamine levels are higher in individuals with panic disorders than in those without, and contribute to the clinical syndrome. These individuals might, therefore, be predisposed to greater norepinephrine and epinephrine surges in response to stressors.[59] A study of circulating microRNA profiles in patients with Takotsubo syndrome showed striking differences from patients with STEMI, who acted as controls.[60] In particular, higher levels of the miR-16 and miR-26a microRNA precursor families have been associated with neuropsychiatric disease.[61,62] Pre-existing anxiety disorders might need to be considered in management strategies to avoid syndrome onset after future stressful episodes.

The second phase is the cardiovascular response to surge in circulating catecholamines. Several hypotheses have been proposed to explain the association with Takotsubo syndrome. The three most prominent hypotheses—multivessel vasospasm, direct catecholamine-mediated myocardial stunning, and increased ventricular afterload—are discussed below. Of note, these hypotheses are unlikely to be mutually exclusive, given the exposure of the entire cardiovascular system to the catecholamine storm. Although a diverse range of experimental and clinical observations have been reported, they likely share a common end point of acute apical dysfunction (Figure 2). For example, multivessel vasospasm driven by high norepinephrine and epinephrine levels via α-adrenoceptors in the vasculature and catecholaminergic myocardial stunning driven by β-adrenoceptor signalling could plausibly coexist, with the latter modifying the myocardial response to ischaemia via activation of cardioprotective signalling pathways.[57] The impact of peripheral vascular responses with vasoconstriction, systemic arterial hypertension, and increased afterload versus vasodilatation, hypotension, and reduced afterload might also be relevant in determining the anatomical variant and the susceptibility of

the patient to complications such as acute left ventricular outflow tract obstruction that could further exacerbate the developing acute failure syndrome.[63]

Acute multivessel coronary spasm

Many of the initial cases of Takotsubo syndrome in Japan showed multivessel vasospasm on diagnostic coronary angiography. In subsequent series, the presence of vasospasm was variable, but spontaneous vasospasm was reported in 5–10% of cases.[62,64] Vasospastic provocation during the acute phase of Takotsubo syndrome has been studied in several series, with positive results being reported in 10–43% of patients.[65,66] In other studies, epicardial coronary vasospasm was less prominent, whereas microvascular dysfunction was more common.[67] A review of nine cohort studies concluded that provocation-induced vasospasm was present in 34 (28%) of 123 patients.[66] One group reported that inducible vasospasm with acetylcholine provocation at follow-up led to recapitulation of acute apical dysfunction, which supports the potential role of multivessel vasospasm, in at least some patients with the apical variant.[69]

Various studies suggest that endothelin levels are higher in patients with acute Takotsubo syndrome compared with patients with acute MI.[60] Endothelin is an extremely potent vasoconstrictor, and could be a potential mechanism to trigger multivessel vasospasm. In addition, after any stress and surge in catecholamines, generalised impairment of endothelial function secondary to oxidative stress is expected. Coronary and peripheral arteries might, therefore, be prone to vasospasm upon provocation. The distinction between cause and association is important to clarify, because vasospasm correlates with the region of dysfunction in some but not all patients, leading some authors to conclude that vasospasm has no causal role.[64] Anatomical abnormalities of coronary arteries, such as myocardial bridging[70] and hypoplastic coronary arteries,[71] have also been observed in patients with Takotsubo syndrome, but no evidence supports causative roles.

Several reported clinical cases were triggered by dobutamine,[72] which is a vasodilator with minimum vasospastic effects, or by epinephrine, which also has a dominant coronary vasodilatory effect. Likewise, in preclinical models, high doses of the β-adrenoceptor agonist isoproterenol has triggered acute apical dysfunction.[73] These findings do not support vasospasm as the primary mediator of Takotsubo syndrome. In addition, studies have shown normal myocardial perfusion in patients assessed with bubble-contrast echocardiography during the development of apical dysfunction after isoprenaline injection.[74] Histopathological features of endomyocardial biopsy samples taken from patients with Takotsubo syndrome show patterns of myocardial abnormalities not associated with infarcted, stunned, or hibernating myocardium.[49] A primary vascular cause, therefore, seems unlikely.

Catecholamine-mediated myocardial stunning

Various groups have suggested that the surge of circulating catecholamine has a direct effect on the ventricular myocardium that can result in apical ballooning, typical of Takotsubo syndrome. Several years ago, Lyon and colleagues[57] proposed a hypothesis to explain the anatomical pattern of myocardial dysfunction in acute Takotsubo syndrome. The β2-adrenoceptor hypothesis is based on the observation of apical–basal gradients of sympathetic nerve endings and β-adrenoceptors in mammalian hearts. In several mammalian species, including humans, higher sympathetic nerve density is seen in the basal myocardium than in the apex.[75] The location of cardiac sympathetic nerve terminals, therefore, does not explain apical hypokinesia, the most common anatomical variant of Takotsubo syndrome, although this feature might have a role in the basal variant. By contrast, in several studies of nonhuman mammalian hearts, the density of β-adrenoceptors is highest in the apical myocardium of the left ventricle. This region, therefore, is most sensitive to circulating catecholamines, including exogenous catecholamine administration,[76–78] but whether similarities exist in human hearts remains to be clarified.

The opposing apical–basal sympathetic nerve and β-adrenoceptor gradients ensure balanced myocardial responses to normal levels of sympathetic activation, for example during exercise or mild stress, when epinephrine is generally a positive inotrope. However, a bell-shaped dose–response relationship has been demonstrated for myocardial contraction. In the context of extreme stress, when circulating epinephrine reaches high levels, the β-adrenoceptor gradient makes the apical myocardium most sensitive to the negative inotropic effects of epinephrine.[79,80] This pharmacological property of the β-adrenoceptor is known as stimulus trafficking, where high epinephrine levels result in a switch from the stimulatory $G_s\alpha$ pathway to the cardioinhibitory $G_i\alpha$ secondary messenger pathway within the cardiomyocyte.[57,79] β2-adrenoceptor activation of the $G_i\alpha$ pathway leads to cardioprotective apoptosis via several other pathways,[81] which might minimize the toxic effects of vasospastic ischaemia, pressure-induced injury from high intracavity pressures, and excessive catecholaminergic stimulation on the myocardium. Of note, β2-adrenoceptor-activated $G_i\alpha$ signalling has been demonstrated in chronic heart failure in human hearts. Although activation of these pathways has been noted in myocardial biopsy samples from patients with Takotsubo syndrome, it has yet to be confirmed in the acute phase. The hypothesis was tested in a rat model of Takotsubo syndrome where reversible apical hypokinesia was induced with high-dose epinephrine.[78] Takotsubo syndrome could be prevented by pretreatment with the $G_i\alpha$ protein inhibitor pertussis toxin.[78] The findings were replicated in another preclinical model, where pertussis toxin prevented acute apical dysfunction induced by high-dose isoprenaline injection, although mortality was high.[73] Computer modelling studies have been conducted to evaluate the effect of varying β-adrenoceptor gradients across the left ventricle under different haemodynamic situations, and were able to replicate the acute apical dysfunction observed when the β-adrenoceptor density was highest at the apex.[82]

Excessive transient ventricular afterload

The peripheral circulatory and systemic responses to acute catecholamine administration are dramatic, whether observed clinically or in the research laboratory. In the rat epinephrine model,[78] within seconds of intravenous epinephrine injection, severe peripheral vasoconstriction caused a surge of systolic and diastolic blood pressure. Peak systolic pressure was initially >250 mmHg and diastolic pressure was >100 mmHg, which activated the vagal reflex and resulted in sinus bradycardia.[78] This severe hyperacute arterial hypertension lasts only a few minutes, during which the heart is in a hypercontractile state. In a clinical case report of Takotsubo syndrome, the authors described a similar hyperacute phase of hypertensive crisis associated mainly with basal hyperkinesis.[83] Hypertensive crises have also been frequently observed in patients with subarachnoid haemorrhage and phaeochromocytoma. The physiological state evolves into a secondary phase when acute apical dysfunction develops on a background of normotension or hypotension, and is frequently complicated by cardiogenic shock and either persistent vasoconstriction or paradoxical vasodilation.[34]

Consideration of these temporal phases is important when interpreting clinical and preclinical observations, and when assessing the role of haemodynamics and ventricular–arterial coupling.[84] The increase in wall stress imparted by high intracavity pressures might initiate regional dysfunction. The potential for the hypertensive storm to cause acute myocardial dysfunction has been explored with various catecholamines and has produced some intriguing findings.[63] Administration of primary vasoconstrictors, to cause high afterload, frequently activated the inverted or basal Takotsubo variant. Triggering of coronary vasospasm and apical dysfunction might be expected, but was not seen.[63] By contrast, catecholamines that reduce peripheral vascular resistance via vasodilation, which led to lower systolic blood pressure and ventricular afterload, were more likely to cause the typical apical variant.[83] This finding is of interest because some patients have systemic arterial vasodilatation and low systemic vascular resistance, which might reflect maladaptive regulation by the peripheral sympathetic nervous system.[34,85] These features are usually measured hours after the initial stressful trigger and catecholamine surge and, therefore, whether they are present in the acute phase remains to be clarified. Abnormalities of peripheral sympathetic nerve function and arterial vasomotor regulation occur in the aftermath of the acute catecholamine storm.[34,63,85,86] Vasodilating catecholamines might activate myocardial as well as vascular β2-adrenoreceptors, which could lead to a vasodilatory effect.

The acute ventricular afterload insult followed by the reduction in contractile responses could conceivably occur in concert and result in the clinical pattern of apical dysfunction. Some individuals could be more susceptible to one pathophysiological mechanism. For example, individuals with Takotsubo syndrome were found to be carriers of the *GRK5* Leu41Gln polymorphism, which is a gain-of-function polymorphism for G protein-coupled receptor kinase 5.[87] This kinase phosphorylates β2-adrenoceptors and activates stimulus trafficking. Individuals harbouring this polymorphism, therefore, could be at risk of developing negative inotropic responses to epinephrine at lower levels than noncarriers and could have greater vasodilatory responses.[88] These two features in combination would potentially lower the threshold for inducing apical dysfunction in the context of acute stress. Nevertheless, no other genetic studies have replicated this finding[89] and, therefore, this effect might be a relative susceptibility effect rather than an absolute causal genetic effect.

Postmenopausal hormonal status

Given the central role of catecholamines and the strong predisposition for occurrence of Takotsubo syndrome in postmenopausal women, the potential role of chronic oestrogen exposure and loss of the sympatholytic effects of oestrogen should be considered. Oestrogen reduces the inotropic and chronotropic response to catecholamines, alters vascular reactivity, and is cardioprotective.[90–92] Several studies demonstrate that myocardial β-adrenoceptor-mediated positive inotropic responses are greater in male hearts than in age-matched female hearts, and that these differences are mediated by reduced β1-adrenoceptor signalling in women. Similarly, reduced myocardial β1-adrenoceptor signalling in ovulating women seems to be protective against myocardial insults, including stress-induced catecholamine production and ischaemia–reperfusion injury.[30,93] Oophrectomy removes this protective effect in preclinical models, and is associated with an increase in β1-adrenoceptor signalling and inotropy. In an animal model of stress-induced Takotsubo syndrome by conscious restraint, oestrogen supplementation to oophrectomy reduced the apical dysfunction observed during stress.[31,90] Raised oestrogen concentrations is also associated with increased vascular β2-adrenoceptor-mediated vasoreactivity, and their loss following menopause could lead to greater vasoconstriction with reduced β2-adrenoceptor-mediated vasodilatation in the setting of high stress-induced surges in catecholamines.

Conclusions

Takotsubo syndrome is an acute cardiac syndrome characterized by transient left ventricular dysfunction in more than one coronary artery territory, and often in a circumferential apical, mid-ventricular, or basal distribution. Awareness that these variants are not mutually exclusive and that the reversible apical myocardial dysfunction observed could result from more than one pathophysiological phenomenon is growing. There remains much to learn regarding the epidemiology and the underlying pathophysiology of this condition in order to improve diagnostic and treatment pathways. Further research is required to help clarify the hypotheses discussed and to increase our understanding of the cardiovascular responses to acute stress and the pathophysiology underpinning Takotsubo syndrome.

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