Mechanisms of stress (Takotsubo) cardiomyopathy

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Abstract | Stress cardiomyopathy, also referred to as Takotsubo cardiomyopathy, transient apical ballooning or broken heart syndrome, is a disorder associated with transient left ventricular dysfunction. Symptoms include acute chest pain and dyspnea accompanied by electrocardiographic changes, such as ST-segment elevation and T-wave inversions, minimal elevation of cardiac enzyme levels and transient wall-motion abnormalities in the absence of substantial coronary artery obstruction. Complete recovery of contractile function has been documented in nearly all cases, but the mechanisms of disease remain unclear and the cause has not been established. Coronary artery vasospasm, microcirculation dysfunction, and transient obstruction of the left ventricular outflow tract have been proposed as possible causes of this disorder. An excessive release of catecholamines also seems to have a pivotal role in the development of stress cardiomyopathy. This Review summarizes published data on stress cardiomyopathy, focusing primarily on the most likely causes of this cardiac entity.

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Introduction

Stress cardiomyopathy, also known as Takotsubo cardiomyopathy, transient apical ballooning or broken heart syndrome, has aroused interest in the cardiology community since it was first described by Dote *et al.*, who named it Takotsubo because the shape of the left ventricle resembles a Japanese octopus trap, with a round bottom and narrow neck.[1] Symptoms occur after emotional or physical stress[2–4] and are similar to those seen in acute myocardial infarction, including sudden onset of chest pain associated with convex ST-segment elevation, and a moderate increase in creatine kinase and troponin levels.[2,5] A diagnosis of obstructive coronary artery disease can be excluded, however, in the presence of severely depressed left ventricular function. Variant forms of left ventricular dysfunction have been reported, including wall-motion abnormalities, such as midventricular ballooning with sparing of the basal and apical segments, or inverted Takotsubo (Figure 1).[6–9] Involvement of the right ventricle is common in stress cardiomyopathy and associated with more severe left ventricular dysfunction.[10–12] Any form of contractile dysfunction is transient and reversible, however, with resolution generally achieved within days or weeks.[3,13]

The prevalence of stress cardiomyopathy among patients with symptoms suggestive of myocardial infarction is 0.7–2.5%, and it is found predominantly in postmenopausal women (90%).[3,14,15] The prognosis of stress cardiomyopathy is favorable,[3] although fatal complications, such as cardiogenic shock, malignant arrhythmias and free wall rupture of the left ventricle, have been reported.[16–20] The in-hospital disease-related mortality rate is 2%.[21] Although patients with stress cardiomyopathy have a similar 4-year cardiovascular survival to people from the general population matched for age and sex, an association with malignancies has been demonstrated in approximately 50 patients, potentially as a result of paraneoplastic phenomena.[21,22]

No large studies have confirmed the etiology of stress cardiomyopathy, so determining the underlying cause has so far not been possible.[23] Several pathological mechanisms have been proposed, including coronary artery vasospasm, coronary microcirculation dysfunction, obstruction of the left ventricular outflow tract (LVOT), and catecholamine overload.[24–27] Published data suggest that substantially elevated plasma catecholamine levels seen in stress cardiomyopathy patients could be particularly relevant, and result in catecholamine-related toxic effects.[2,11,27–30] This Review primarily addresses the pathological mechanisms of stress cardiomyopathy and provides an overview of data relating to this cardiac entity.

Vasospasm of coronary arteries

Various forms of left ventricular dysfunction are reported in stress cardiomyopathy, such as apical ballooning and midventricular dysfunction, but the underlying causes have not been fully elucidated. Myocardial stunning, where brief periods of ischemia owing to vasospasm lead to transient structural, metabolic and functional abnormalities, has been suggested as a cause of symptoms.[31] Dote *et al.* were the first to suggest this link when they presented five patients with stress cardiomyopathy who had chest pain and electrocardiographic abnormalities,

Competing interests
The authors declare no competing interests.

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Key points

- Stress cardiomyopathy occurs in 0.7–2.5% of patients presenting with the symptoms of acute coronary syndromes
- Postmenopausal women are the group predominantly affected by stress cardiomyopathy
- Although the cause of stress cardiomyopathy is still unknown, excessive catecholamine levels have a major role in the pathology of this disorder
- Catecholamine overload results in substantial structural alterations, including increased extracellular matrix, contraction band necrosis, and mild neutrophil infiltration
- Stress cardiomyopathy is associated with increased oxidative stress and the alteration of Ca^{2+}-handling proteins, which might be crucial for contractile dysfunction
- An activated cell survival cascade, such as the PI3K–AKT pathway, could protect cardiomyocytes from cell death and contribute to their rapid regeneration in patients with stress cardiomyopathy

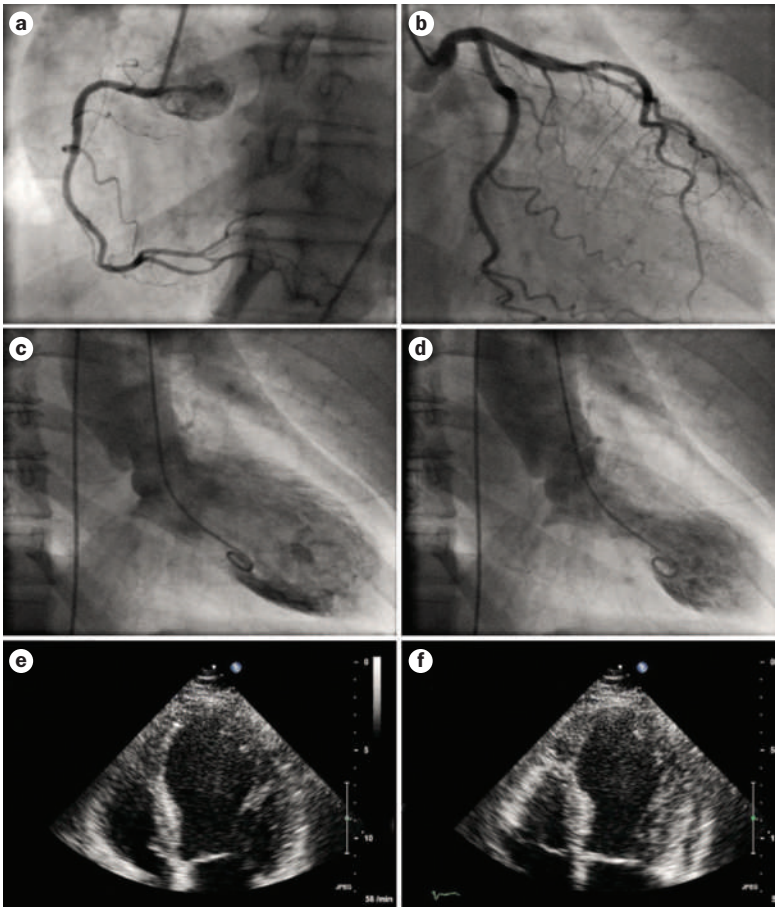

Figure 1 | Coronary angiography in patients with stress cardiomyopathy. Obstructive coronary artery disease was not seen in the **a** | right coronary artery or **b** | left coronary artery. Typical apical ballooning during the systolic phase is seen on left ventriculography (**c** | diastole, **d** | systole). Echocardiography findings confirm left ventricular wall motion abnormalities during **e** | diastole and **f** | systole.

but no coronary artery stenoses.[1] Electrocardiographic studies indicate impaired blood flow in patients with stress cardiomyopathy, in whom findings were similar to those in patients with acute coronary syndromes.[32] However, impaired blood flow seems an unlikely major cause, as spontaneous coronary vasospasm has since been reported in only 2% of patients with stress cardiomyopathy.[4] Moreover, each area of abnormal left ventricular wall motion extends beyond that normally perfused by a single coronary artery.[33] Also, in none of the patients described hitherto was there definite evidence for an obstructive or flow limiting lesion on coronary angiography performed immediately after the onset of symptoms.[34] Finally, histological alterations described in stress cardiomyopathy, including mild inflammatory cell infiltration, considerable increase in extracellular matrix protein, and contraction band necrosis,[11] are not observed in patients with ischemic myocardial stunning alone.[35] A single pathological mechanism for both disorders, therefore, remains questionable. Impaired coronary blood flow owing to plaque rupture has been suggested as a cause of stress cardiomyopathy in the absence of coronary vasospasm.[36]

Some investigators have used provocative tests, such as infusion of ergometrine or acetylcholine to evaluate the frequency of inducible coronary vasospasm in stress cardiomyopathy, with inconclusive results. A review of the existing literature showed that multivessel vasospasm could be induced in 24 (28.6%) of 84 patients with stress cardiomyopathy (95% CI 20–39%).[3] This finding was confirmed by another literature review that showed positive provocative test results in 27.6% of 28 patients with stress cardiomyopathy.[37] It is, therefore, difficult to determine whether myocardial stunning as a result of epicardial coronary artery vasospasm is an underlying or main cause of stress cardiomyopathy.

Disturbance of the microcirculation

Disorder of the microcirculation has been proposed as an underlying mechanism of stress cardiomyopathy. Kume *et al.* demonstrated microcirculation disturbances in patients with stress cardiomyopathy by use of Doppler flow-wire assessment.[38] Correspondingly, TIMI (Thrombolysis in Myocardial Infarction) frame counts, a validated index of coronary blood flow,[39] were significantly higher in all coronary arteries of patients with stress cardiomyopathy compared with control patients ($P<0.01$); although TIMI frame counts did decrease, they remained high in patients even after resolution of left ventricular dysfunction.[40] This finding was confirmed by Bybee *et al.*, who performed TIMI counts and coronary angiographic assessments at hospital admission in 16 women with stress cardiomyopathy.[41] The TIMI frame counts were abnormal in every patient, and often abnormal in all three major coronary vessels. Impaired myocardial perfusion correlated with the extent of myocardial injury. Echocardiographic findings also showed a reduced coronary flow reserve with early recovery during the subacute assessment on day 7. These findings are indicative of diffuse coronary microvascular dysfunction and could be a result of a surge in catecholamine secretion, inducing microvascular endothelial damage through β1-adrenoceptor activation. Whether coronary microvascular dysfunction is a primary mechanism in the pathogenesis of stress cardiomyopathy, or is simply

an associated, secondary phenomenon, is, however, unclear.[42] Limited vasodilatory capacity of the coronary microcirculation has been documented in patients with idiopathic dilated cardiomyopathy;[43] the microcirculation disturbance observed in stress cardiomyopathy could, therefore, occur as a result of left ventricular dysfunction followed by neurohumoral activation.

Obstruction of the LVOT

Early studies showed that LVOT obstruction might be present in patients with stress cardiomyopathy. A systematic analysis of the literature demonstrated LVOT obstruction in 25% of patients, all of whom presented with septal bulge associated with systolic anterior motion of the mitral valve and mitral regurgitation.[44] This morphology of the ventricular septum is mostly present in elderly patients and seems to be an important factor for LVOT obstruction in stress cardiomyopathy, mimicking hypertrophic obstructive cardiomyopathy.[44] Additional reports have confirmed structural abnormalities associated with LVOT obstruction, such as mid-ventricular septal thickening, particularly in elderly women.[25] This feature could lead to the development of severe, transient left ventricular mid-cavity obstruction in the presence of increased catecholamine levels.[25] Because the incidence of LVOT obstruction in stress cardiomyopathy is low, however, it remains uncertain whether these changes are a consequence rather than a cause of stress cardiomyopathy.

Catecholamine-mediated effects

Clinical findings

Exposure to endogenous (emotional, related to a pre-existing condition) or exogenous (trauma, surgical procedure, exacerbation of a pre-existing condition) stress and increased sympathetic activity has been reported in most cases of stress cardiomyopathy. This association suggests that the mechanism of disease might be sympathetically mediated. Akashi *et al.* were the first to describe elevated serum catecholamine levels in patients presenting with stress cardiomyopathy.[13] Accordingly, plasma catecholamine concentrations were around two to three times higher in patients with stress cardiomyopathy than in patients hospitalized for acute myocardial infarction (Killip class III).[27] Similarly, norepinephrine levels were notably higher in critically ill patients who also had stress cardiomyopathy than in those without stress cardiomyopathy.[45] Administration of epinephrine at suprapharmacological doses has led to induction of stress cardiomyopathy in two cases, which might support the hypothesis that elevated catecholamine levels are an important etiological factor.[46,47] Excessive catecholamine production in patients with pheochromocytoma, a tumor of the adrenal gland, is also known to induce reversible left ventricular dysfunction.[48]

Nuclear imaging could provide further support for a role of the sympathetic nervous system in stress cardiomyopathy. In one case of a woman with stress cardiomyopathy, PET showed acute retention of ^{11}C-hydroxyephedrine in segments of the left ventricle with contractile dysfunction, which is compatible with increased sympathetic activity.[49] In a study of eight patients with stress cardiomyopathy, decreased ^{123}I-metaiodobenzylguanidine uptake on single-photon emission CT suggested the existence of cardiac autonomic damage and accelerated cardiac sympathetic nervous function in patients.[50]

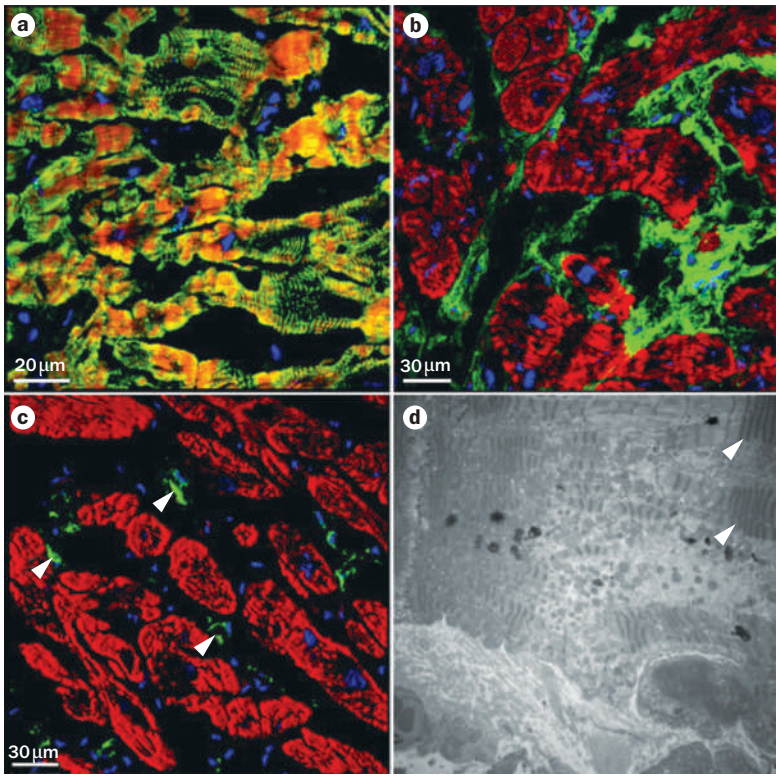

Figure 2 | Myocytes from patients with stress cardiomyopathy. **a** | α-actinin was immunolabeled using the EA53 antibody, F-actin (red) was visualized with TRITC-conjugated phalloidin and nuclei (blue) were counterstained with Draq5™. Note that α-actinin is either absent in the central part of the myocytes or found in a punctuated pattern, which is in contrast to the clear, cross-striated pattern usually seen in control myocardium (not shown). **b** | The extracellular matrix was stained for collagen-1 (green) and showed a marked increase compared with control myocardium (F-actin, red; nuclei, blue). **c** | CD68-positive macrophages (green, arrows) were regionally increased within the tissue biopsy compared with control myocardium (F-actin, red; nuclei, blue). **d** | Electron microscopy showed that the arrangement of cytoskeletal and contractile proteins dissolved. The content of the contractile material was reduced and mainly detected in the border area of the myocytes. Contraction bands were also observed (arrows). Reprinted from *International Journal of Cardiology* **130**, Nef, H. *et al*. Sympathoadrenergic overstimulation in Tako-Tsubo cardiomyopathy triggered by physical and emotional stress. 266–268 © 2008, with permission from Elsevier.

Molecular findings

Stress cardiomyopathy is characterized by morphological alterations that are similar to those following catecholamine cardiotoxic effects reported in animals[51] and humans.[52] Typical structural changes as a result of catecholamine overload include increased production of extracellular matrix, contraction band necrosis (a unique form of myocyte injury that follows exposure to high levels of catecholamines) and mild neutrophil infiltration (Figure 2).[11]

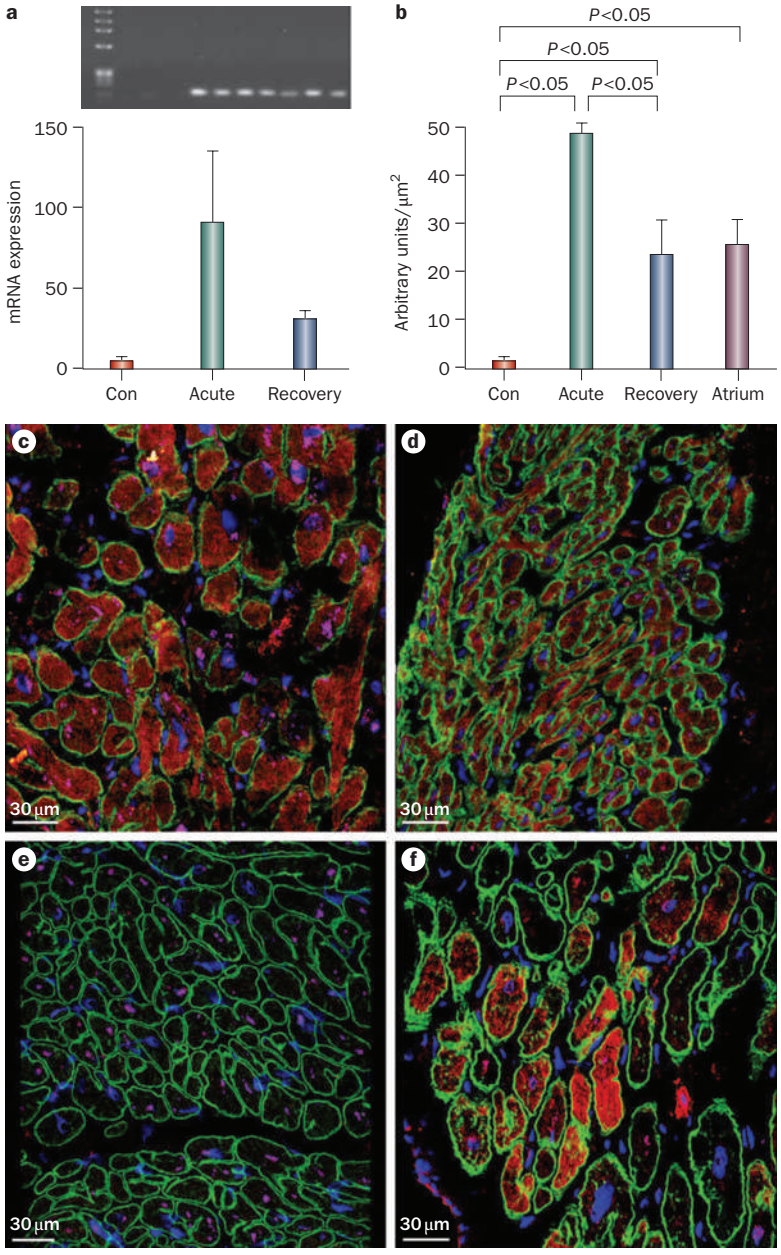

Figure 3 | PCR and immunostaining of tissue biopsies from patients with stress cardiomyopathy. Sarcolipin is overexpressed in patients with stress cardiomyopathy as determined by **a** | PCR and **b** | immunostaining. Sarcolipin (red) showed significant upregulation in the **c** | phase of severely depressed contractile function (acute) compared with in **d** | tissue after functional recovery. Specific labeling did not reveal sarcolipin expression in the **e** | healthy left ventricle, but it is expressed in **f** | the healthy left atrium. Abbreviations: Con, control; SLN, sarcolipin. Nef, H. *et al.* Abnormalities in intracellular Ca^{2+} regulation contribute to the pathomechanism of Tako-Tsubo cardiomyopathy, *European Heart Journal* 2009, **30** (17), 2155–2164, by permission of Oxford University Press.

Catecholamine overload leads to a variety of cellular responses. An extracellular accumulation of collagen α-1 (I) chain and, consequently, an increased ratio of collagen α-1 (I) chain to collagen α-1 (III) chain accounts for a large and rapid increase in fibrosis. Levels of reactive oxygen species and the profibrotic mediator angiotensin II are also increased.[53] Catecholamines can also activate transforming growth factor β, its stimulating factor connective tissue growth factor, and osteopontin. Matrix metalloproteinase (MMP)-2 and MMP-9 are not correspondingly activated, however, so the augmentation of extracellular matrix proteins results in myocardial disarray.

Disturbance of the calcium regulatory system has been demonstrated in stress cardiomyopathy. This effect might be caused by supraphysiological levels of catecholamines, which stimulate β-adrenoceptors and alter the expression of calcium-regulatory protein genes.[54,55] Sarcolipin regulates sarcoplasmic/endoplasmic reticulum calcium ATPase 2 (SERCA2) by lowering its affinity for Ca^{2+} and is frequently overexpressed in stress cardiomyopathy. Two independent reports have described slowed cardiomyocyte relaxation and impaired cardiac function in mice overexpressing sarcolipin.[56,57] Thus, raised sarcolipin expression in stress cardiomyopathy could contribute to contractile dysfunction in the acute phase (Figure 3). The question remains whether ventricular expression of sarcolipin is detrimental in the acute phase, as its expression persists after functional recovery, albeit to a lower level.[28] The inhibitory effect of sarcolipin on SERCA2 is substantially increased if it binds via its related protein, phospholamban, rather than by direct binding.[28,57] The interaction of these proteins is not fully understood, however, and requires further clarification.

There is no evidence to suggest that alterations in the expression of calcium-handling proteins are responsible for the acute deleterious effects of stress cardiomyopathy. Intense G-protein-stimulated β1-adrenergic receptor and β2-adrenergic receptor signaling is, however, responsible for initiating changes in gene expression. Infusion of a β-adrenergic receptor agonist reduced expression of SERCA2 messenger RNA levels in animal models.[58] Furthermore, α1-adrenergic receptor (a Gq-coupled receptor) and G-protein-stimulated β1-adrenergic receptor signaling can directly modulate gene expression via the cyclic AMP-responsive element binding protein 1 and calcineurin–nuclear factor of activated T cells signaling pathways, which are known to cause changes in *ATP2A2 (SERCA2)* gene expression.[59] Excessive signaling by β1-adrenergic receptor and cyclic AMP-dependent protein kinase catalytic subunit α (PKA C-α) could explain the cardiotoxicity observed in patients with stress cardiomyopathy as a result of cardiomyocyte calcium overload, mitochondrial calcium overload, reactive oxygen species production and oxidative stress.[60]

At normal physiological epinephrine concentrations, epinephrine binding to β2-adrenergic receptors activates the PKA C-α pathway, resulting in a positive inotropic response.[60] At supraphysiological concentrations, however, epinephrine has a negative inotropic effect on myocyte contraction.[61] This change in response may result from a switch in β2-adrenergic receptor coupling, from stimulatory G-protein signaling to inhibitory G-protein signaling, a process called stimulus trafficking.[60,62] β2-adrenergic receptor–inhibitory G-protein coupling is also known to activate the PI3K–AKT-signaling

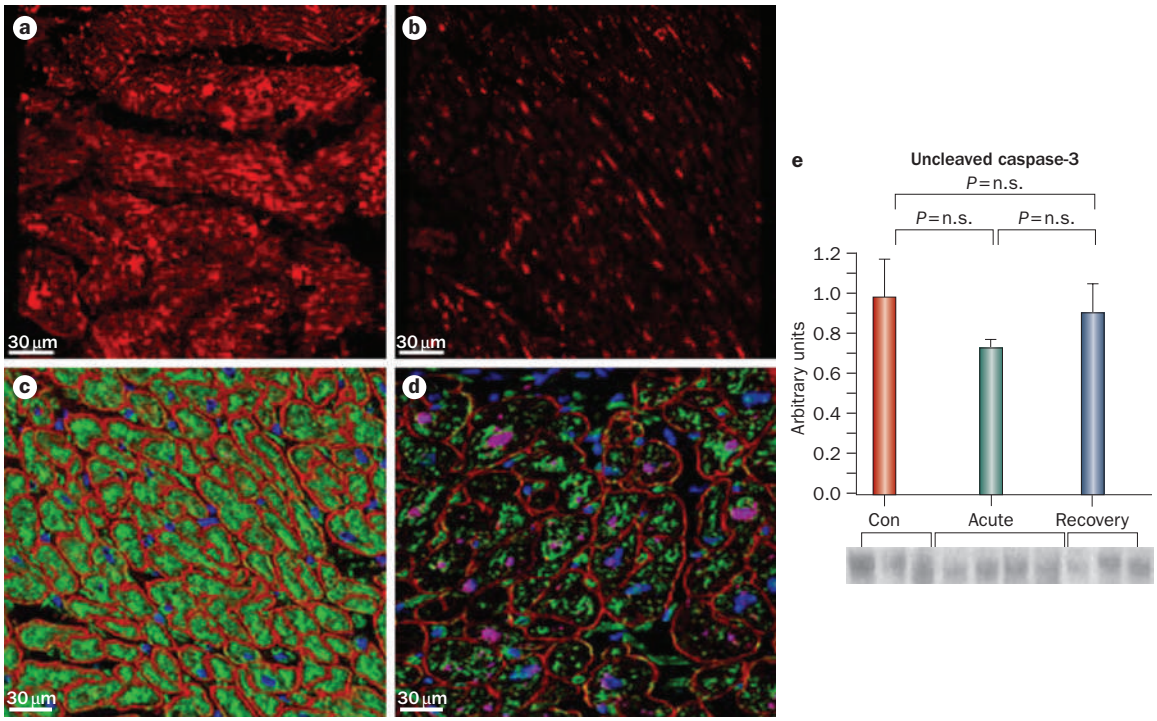

Figure 4 | Superoxide production in patients with stress cardiomyopathy. Superoxide production was characterized by dihydroethidium staining of tissue in **a** | the acute phase of stress cardiomyopathy and **b** | after functional recovery. IκB (green) was detected in **c** | left ventricular control tissue compared with **d** | strong degradation of IκB in patients with stress cardiomyopathy, serving as indirect evidence for the activation of NFκB. **e** | Apoptotic activity is not significantly altered in stress cardiomyopathy. Abbreviations: Con, control; IκB, inhibitor of nuclear factor kappa B; NFκB, nuclear factor kappa B; n.s., nonsignificant. Reprinted from *Journal of Molecular and Cellular Cardiology* **44**, Nef, H. *et al*. Expression profiling of cardiac genes in Tako-Tsubo cardiomyopathy: insight into a new cardiac entity. 395–404 © 2008, with permission from Elsevier.

pathway. This pathway is activated in stress cardiomyopathy, thereby contributing to the favorable outcome of this disorder by activating antiapoptotic genes, such as *NFκB1* and *BCL2*, and promoting cell survival. Signaling of activated PI3K–AKT and the mammalian target of rapamycin (mTOR) is also associated with increased protein biosynthesis, which is essential for myocardial regeneration (Figure 4). The increased expression of osteopontin could trigger the observed transformation of fibroblasts to myofibroblasts in stress cardiomyopathy and might, therefore, have a protective role by minimizing myocardial disarray.

Models of stress cardiomyopathy

Most clinical studies of stress cardiomyopathy have involved very small numbers of patients, been largely carried out in a single institution, and the findings have not been replicated. The development of animal models is, therefore, important to investigate the molecular mechanisms of this syndrome. Reversible left ventricular dysfunction and ST-segment elevation can be reproduced in the immobilization stress test—a model of emotional stress in rats. These changes are accompanied by profound sympathoadrenal activation comparable to that seen in patients with stress cardiomyopathy.[27,63] Upregulation of immediate early genes, molecular markers of cellular activation and transcriptional factors have been shown in the immobilization stress test.[64] When these results are compared with the gene expression profiles of patients with stress cardiomyopathy, it shows that the overexpression of genes involved in oxidative stress are a possible link.[53] These physiological and molecular alterations were attenuated by pretreatment with α-blockers and β-blockers, thus supporting the hypothesis of catecholamine involvement in stress cardiomyopathy.[65] A study by Khullar *et al.* used a model of catecholamine-induced cardiomyopathy by administering norephinephrine to rhesus monkeys 2 h daily for 3 consecutive days.[66] The animals were sacrificed 2 h (acute phase), 48 h (subacute phase), or 21 days (chronic phase) after the last infusion. The histopathological examination revealed myofibrillar degeneration, myocytolysis and vacuolization with aggregation of lymphmononuclear cells in the acute phase.

Hormones in stress cardiomyopathy

The ovarian sex hormones estrogen and progesterone have important roles in the regulation of myocardial contraction. Expression of the estrogen receptor on cardiac myocytes could explain the direct effect of female hormones on cardiac contractility.[67] Accordingly, estrogen has been shown to alter calcium uptake in myocytes; SERCA2 expression was remarkably downregulated in ovariectomized rats compared with that in sham

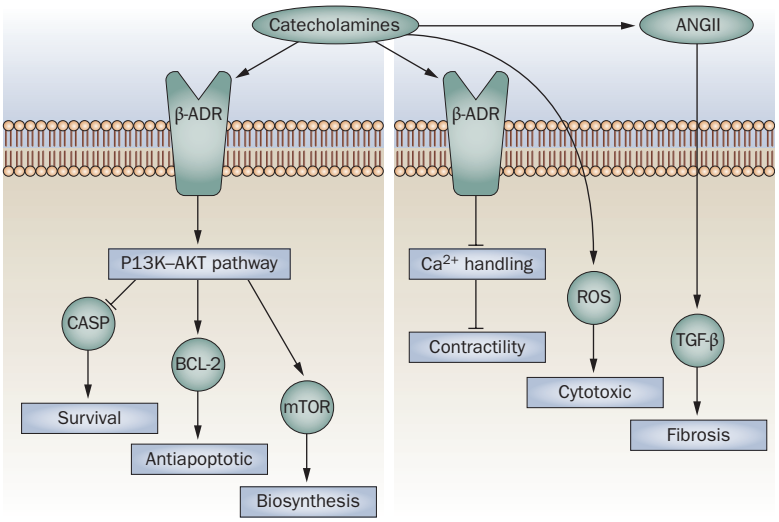

Figure 5 | The pathomechanistic concept of stress cardiomyopathy. Overexpression of catecholamines following a stress event leads to a number of changes that can have either protective or adverse effects. Abbreviations: β-ADR, β-adrenergic receptor; ANGII, angiotensin II; CASP, caspase; mTOR, mammalian target of rapamycin; PI3K–AKT, phosphatidylinositol 3 kinase–AKT; ROS, reactive oxygen species; TGF-β, transforming growth factor β.

animals.[68] Moreover, the activity of SERCA2 was reduced owing to dephosphorylated phospholamban, which has also been observed in stress cardiomyopathy.[25] Whether the deficiency of ovarian sex hormones causes or potentiates disturbance of the calcium regulatory system has yet to be evaluated. Men rarely develop stress cardiomyopathy yet are physiologically estrogen-deficient, which suggests that this syndrome is not due to ovarian hormone deficiency. Nonetheless, the effects of hormone deficiency on contractility in the presence of excessive catecholamine levels needs further clarification.

Conclusions

Stress cardiomyopathy is characterized by severe, but transient, left ventricular dysfunction. Data suggest that catecholamine overload plays a central role in the development of this disorder by causing morphological alterations and disturbance of Ca^{2+} homeostasis. Several protective mechanisms, including PI3K–Akt signaling could be responsible for rapid regeneration of cardiomyocytes and the mostly benign prognosis of stress cardiomyopathy (Figure 5). Since the first description of stress cardiomyopathy, an impressive body of data has been collected—the puzzle of stress cardiomyopathy still awaits completion, however, and further research is needed to fully understand this disorder.

Review criteria

This Review was based on a thorough search of evidence-based sources of information, including the Cochrane Database of Systematic Reviews and a comprehensive MEDLINE search with the MeSH terms "Tako-Tsubo cardiomyopathy", "stress cardiomyopathy" and "apical ballooning". Papers cited include English, German and Japanese-language articles published in the past 5 years, as well as some historical references.

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