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Stress-Induced Cardiomyopathy: Clinical Observations

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1. Introduction

Stress-induced cardiomyopathy has achieved global notoriety in only 20 years since it was introduced as “Takotsubo cardiomyopathy” (which means “octopus trap” in Japanese) (Dote et al., 1991). It is also known as “left ventricular apical ballooning”, “ampulla cardiomyopathy” and “broken heart syndrome”. Stress-induced cardiomyopathy is associated with typical electrocardiographic findings and severe chest pain suggesting ST-segment elevation myocardial infarction (STEMI). However, emergency coronary angiography usually does not show significant stenosis or definite flow limitation. In general, left ventricular ejection fraction (LVEF) is markedly depressed and is recovered within the normal range within 1–2 weeks. Most cases have a good outcome and some may not even need further medical therapy if the underlying the cause is uncovered. Several hypotheses have been proposed but the pathophysiologic mechanism is incompletely understood. Here we discuss the clinical findings, diagnostic modalities, possible pathophysiologic mechanisms, prognosis and management of stress-induced cardiomyopathy.

2. History of reporting of stress-induced cardiomyopathy

In 1980, strong evidences implying stress-induced cardiomyopathy were reported via the autopsies of homicidal victims (Cebelin & Hirsch, 1980). They found pathognomonic findings of contraction band necrosis in 11 patients who had died due to a physical assault without internal injuries. One case report revealed that severe emotional stress could bring about deterioration of cardiac function which developed into pulmonary edema (Anon, 1986). Echocardiographic studies demonstrated that left ventricular wall motion abnormalities and myocardial damage could be accompanied by subarachnoid hemorrhage (Pollick et al., 1988). This pioneering work inspired other investigators, who discovered that LVEF and regional wall motion abnormalities were significant predictors of death in patients with subarachnoid hemorrhage (Sugimoto et al., 2008). Reversible left ventricular dysfunction induced by excessive catecholamine surges in pheochromocytoma was also reported (Iga et al., 1989). This finding suggested that catecholamines at high concentrations can directly damage the myocardium.

Stress-induced cardiomyopathy was termed “Takotsubo cardiomyopathy” by Japanese cardiologists in 1991 (Dote et al., 1991). Advances in diagnostic imaging and emergency coronary angiography have contributed to increased recognition of stress-induced cardiomyopathy, and increasing numbers of reports have been published since then.

3. Clinical observations: Single-center experiences

We reported retrospective data of 39 patients diagnosed with stress-induced cardiomyopathy during 5 years in a single center (Lee, J.W. et al., 2010). Our results showed differences from other reports. In our study, 69% of patients were female, and the mean age was 61.3 ± 16.1 years. The most frequent symptom at initial presentation was dyspnea (46%) rather than chest pain (26%). Emotional stress was found in only 15% of subjects. The main triggering factors were physical stress associated with illness (59%), procedure-related complications (8%) and trauma (8%). Initial electrocardiography revealed T-wave inversion (46%), ST-segment elevation (28%) and ST-segment depression (5%). LVEF was recovered from $45 \pm 16\%$ upon hospital admission to $61 \pm 13\%$ upon hospital discharge. The level of B-type natriuretic peptide (BNP) was increased (745.4 ± 905.6 pg/mL) and 23 patients (59%) had elevated levels of highly-sensitive C-reactive protein (hs-CRP; 44 ± 61 mg/L) at initial presentation. The peak level of creatine kinase-MB (CK-MB) fraction and troponin I showed mild elevation (15.6 ± 20.9 ng/mL and 6.8 ± 12.3 ng/mL, respectively).

Echocardiography was shown to be a useful tool to detect transient left ventricular outflow tract (LVOT) obstruction, apical thrombus on the site of apical ballooning, and unusual inverted-type (mid-ventricular) ballooning.

Three patients (8%) died due to pneumonia and 13 patients (33%) experienced cardiogenic shock. Inotropic agents were needed in 10 patients (26%) and 9 patients (23%) required mechanical ventilation. When we assessed the prognostic factors affecting adverse events such as death or shock, LVEF and hs-CRP levels were independent risk factors by multivariate logistic regression analyses (adjusted for age, sex, and other risk factors).

4. Clinical findings

In general, stress-induced cardiomyopathy is characterized by sudden chest pain or dyspnea, ST-segment elevation mimicking acute myocardial infarction (AMI) or deep T-wave inversion, elevated levels of cardiac enzymes or BNP and transient left ventricular systolic dysfunction. Post-menopausal women seem to be more vulnerable to this syndrome. The definition is continually evolving. There are some divergences of opinion on clinical situations and management.

4.1 Age and sex

The elderly seem to be the most vulnerable to stress-induced cardiomyopathy. The mean age for presentation was >60 years (Bybee et al., 2004). However, a case of stress-induced cardiomyopathy in a newborn after fetal distress was caused by the umbilical cord being twisted around the chest and neck (Greco, 2011). The youngest patient we treated was a 26-year-old female. Despite literature suggesting that the elderly are the most affected, recent case reports have shown the possibility of development of stress-induced cardiomyopathy in patients of any age.

The higher prevalence of females is a consistent finding in published series (Bybee et al., 2004). Nevertheless, the reason for this difference in prevalence between males and females is unknown. Stöllerberger & Finsterer suggested two intriguing hypotheses (Stöllerberger & Finsterer, 2011). The first hypothesis is that males have been biologically better protected against the stress-induced cardiotoxicity of catecholamines than females throughout the centuries. They suggested that males were exposed to more physical stress and developed various protecting mechanisms (Stöllerberger & Finsterer, 2011, as cited in Silventoinen et al., 2001). The higher density of adrenergic receptors of cardiomyocytes in males may result in delayed saturation of receptors and improved protection against catecholamine storms (Stöllerberger & Finsterer, 2011, as cited in Leibel et al., 1987). The second hypothesis is that males are biologically less resistant than females against the stress-induced cardiotoxicity of catecholamines. Males comprise 78.9% of sudden cardiac deaths (Fragkouli & Vougiouklakis, 2010) and one of the risk factors for sudden unexplained death in epilepsy patients was being male (Monté et al., 2007). Large-scale cohort studies could provide answers for the age and sex predominance of stress-induced cardiomyopathy.

4.2 Initial presenting symptoms

The most common presenting symptoms of stress-induced cardiomyopathy are chest pain and dyspnea. Not all studies reported the initial symptoms (especially in the case of dyspnea). Nevertheless, chest pain was the cardinal symptom in 185 of 273 patients (67.8%) and dyspnea the second most common symptom in 40 of 225 patients (17.8%) (Gianni et al., 2006). Cardiogenic shock, severe arrhythmia, mental change or syncope may be the initial presentation. Some patients suffer from chest pain and dyspnea; the most frequent symptom of stress-induced cardiomyopathy in patients in our institution was dyspnea.

In our experience, patients with dyspnea had a longer stay in hospital, elevated levels of BNP and hs-CRP, and decreased initial LVEF, but these differences were not statistically significant (Lee, J.W. et al., 2011). A recent prospective study in a tertiary referral hospital demonstrated that chest pain was more frequently observed in the emotional stress group, whereas dyspnea was the presenting symptom in the physical stress group (acute illness and in-hospital surgery/procedure) (Lee, P.H. et al., 2010).

New imaging modalities contribute to the early diagnosis of stress-induced cardiomyopathy. Hence, the proportion of initial symptoms might shift from emotional stress to physical stress.

4.3 Triggering factors

Triggering factors preceding this syndrome are, in general, divided into “emotional stress” and “physical stress”. A wide variety of emotional stressors have been reported, including panic, fear, anxiety, grief and anger (Prasad et al., 2008; Sharkey et al., 2010). These emotional stressors include immediate (“fight-or-flight”) responses and/or sustained responses, which implies the involvement of protective mechanisms of the body via the stress system (neurohormonal interaction) (Balkin & Cohen, 2011).

Among physical stressors, pheochromocytoma, subarachnoid hemorrhage, exposure to catecholamine/beta-agonist drugs and procedure-related events are representative cases associated with catecholamine excess. Other physical stressors include hypoxia, infection, metabolic abnormalities, invasive procedures, and general anesthesia (Park et al., 2010; Prasad et al., 2008; Sharkey et al., 2010). Madhavan et al. suggested the importance of

physical stress (Madhavan et al., 2011). They suggested that patients with physical stressors had significant underlying co-morbidities that may contribute to the development of heart failure. In addition, physical stressors such as postoperative status may be associated with a more sustained surge in catecholamines compared with emotional stress, which may be shortlived (Park et al., 2010).

4.4 Electrocardiographic findings

The most common abnormality on electrocardiography (ECG) is ST-segment elevation resembling STEMI (Prasad et al., 2008). T-wave inversion is usually observed at initial presentation and during the subacute phase. The proportion of ST-segment elevation and T-wave inversion was 208 of 255 patients (81.6%) and 160 of 249 patients (64.3%), respectively (Gianni et al., 2006). Q waves also could be detected in 63 of 198 patients (31.8%). T-wave inversion may resolve over 3–4 months but may occur as early as 4–6 weeks and, in some cases, be present beyond 1 year (Prasad et al., 2009, as cited in Kurisu et al., 2004 and Matsuoka et al., 2003).

One study tried to distinguish stress-induced cardiomyopathy from anterior wall myocardial infarction by simple and non-invasive ECG tests (Jim et al., 2009). They found that if extensive left ventricular dysfunction and precordial ST-segment elevation were observed, the absence of ST-segment depression, or the presence of ST-segment elevation in inferior leads (particularly II \geq III) were suggestive of stress-induced cardiomyopathy. Lead II is the most sensitive and specific for the detection of stress-induced cardiomyopathy because it is relatively protected from the opposing effect of lateral wall ischemia.

4.5 Laboratory findings

The level of troponin I or troponin T and CK-MB fraction is slightly elevated from baseline reference values. BNP levels in plasma are also elevated to various degrees (Lee, J.W. et al., 2010 and Morel et al., 2009).

One case-control study provided a comprehensive analysis of stress hormone and cardiac biomarker profiles in stress-induced cardiomyopathy, and the values were compared with those from patients with STEMI (Madhavan et al., 2009). The major findings were that: (1) levels of BNP were higher in stress-induced cardiomyopathy despite less necrosis of myocytes, similar left ventricular dysfunction and comparable hemodynamics; (2) there was a marked elevation in levels of an inflammatory biomarker (hs-CRP) in a magnitude similar to that seen in patients with STEMI.

Inflammation may have a crucial role in stress-induced cardiomyopathy. Morel et al. demonstrated that inflammatory status was related to the initial impairment of LVEF and to the extent of neurohormonal activation (Morel et al., 2009). Other research teams demonstrated that patients who developed left ventricular apical ballooning due to severe physical stress in the Intensive Care Unit had a higher frequency of sepsis, cardiomegaly, pulmonary edema and hypotension (Park et al., 2005).

One recent prospective study showed that inflammatory mediators and platelet-activity markers could be used to distinguish stress-induced cardiomyopathy from myocardial infarction (Pirzer et al., 2011). Expression of the platelet-activation marker CD62P and plasma levels of interleukin-6 were significantly lower in patients with stress-induced cardiomyopathy compared with myocardial infarction at the time of hospital admission. Plasma levels of interleukin-7 were significantly elevated in patients with stress-induced

cardiomyopathy compared with patients with myocardial infarction 2–4 days after hospital admission.

The plasma concentrations of catecholamines during the acute phase were 2–3-times higher than in patients with AMI and heart failure, and 20-times higher than in normal adults (Wittstein et al., 2005). Uchida et al. also observed elevated levels of plasma epinephrine and norepinephrine in patients with stress-induced cardiomyopathy (Uchida et al., 2010). The plasma half-life of epinephrine is only 3 min (Zeb et al., 2011, as cited in Ferreira & Vane, 1967), so measurement of catecholamines should be conducted at the time of symptom onset.

4.6 Left ventricular systolic dysfunction

Initial left ventricular systolic function is usually impaired upon hospital admission (mean LVEF, 20–49%) and, in general, resolves within days-to-weeks after initial presentation (mean period, 18 days) (Nef et al., 2010). Most patients achieve normal systolic function during hospitalization, but a few fail to reach the normal range (Sharkey et al., 2010). Moreover, a recent study revealed that absence of functional recovery within 1 week (ejection fraction <50%) was an independent factor associated with mortality (Lee, P.H. et al., 2010).

4.7 Co-morbidity

There are no reported associations between stress-induced cardiomyopathy and co-morbidity. Collective data from 14 studies reported a history of hypertension in 43% of patients (108/247), diabetes mellitus in 11% (53/217) and current or past smoking in 23% (23/100). Others include chronic obstructive pulmonary disease, asthma and malignancy.

One observational study showed that patients with stress-induced cardiomyopathy had significantly higher levels of high-density lipoprotein-cholesterol and lower levels of low-density lipoprotein-cholesterol and triglyceride compared with age- and sex-matched patients with myocardial infarction (Gaddam et al., 2011). Hyper-alpha-lipoproteinemia was noted in 2 patients. That study had a major limitation because the study population was small. However, a history of dyslipidemia should be assessed at initial presentation. This result adds evidence that the pathogenesis is not due to atherosclerotic narrowing of epicardial coronary arteries.

4.8 Preferred time of onset

The occurrence of major cardiovascular events is not randomly distributed over time but instead exhibits chronobiological patterns. Stress-induced cardiomyopathy also seems to exhibit a temporal variation of onset, with peaks during the morning and in the summer (Bossone et al., 2011). One study reported that the highest number of cases was found on Monday and the lowest on Saturday. This phenomenon might be because of stress and catecholamine release (Manfredini et al., 2010). However, conclusions are hard to reach because of the relatively small number of patients involved in this study.

5. Imaging modalities and implications

Several imaging tools are used for the diagnosis of stress-induced cardiomyopathy: coronary angiography with left ventriculography, echocardiography, cardiac magnetic

resonance (CMR) and nuclear imaging. Each examination has its own diagnostic value and benefit. One should understand the advantages and disadvantages and select the most appropriate method for the purpose.

5.1 Coronary angiography

Coronary angiography is essential and the only way to rule out obstruction of coronary arteries (especially in cases of ST-segment elevation). The modified Mayo Clinic criteria to diagnose stress-induced cardiomyopathy demand the absence of obstructive coronary artery disease or angiographic evidence of acute rupture of plaques that could be responsible for the observed wall motion abnormalities. A recent report suggested the possible concurrence of coronary artery disease with stress-induced cardiomyopathy (Winchester et al., 2008). Hence, several cases might be excluded because of the presence of coronary artery disease. If coronary atherosclerotic changes are not significant and regional wall motional abnormalities extend beyond a single coronary artery, stress-induced cardiomyopathy should be suspected. The endocardial border can be readily detected by left ventriculography (Fig. 1).

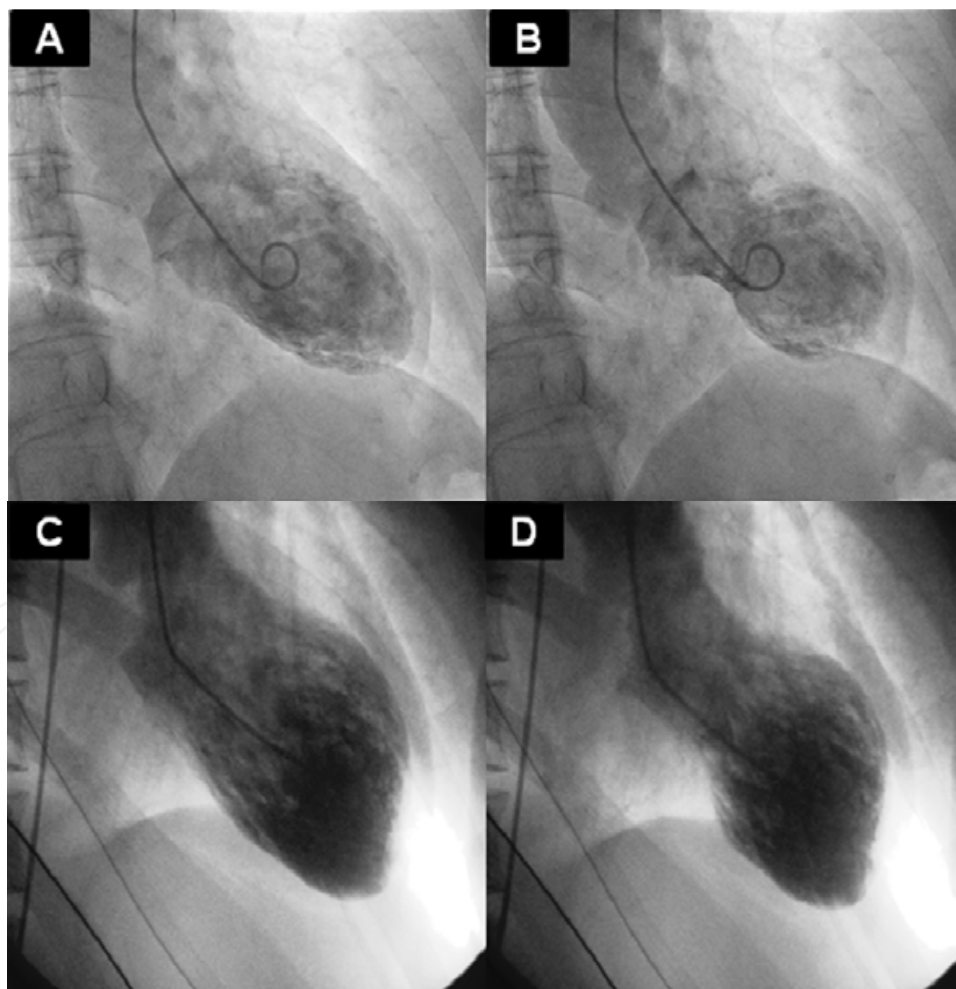


Fig. 1. Left ventriculography shows the typical pattern of apical ballooning with relative basal hypercontractility (A: end-diastole, B: end-systole) and inverted type of mid-ventricular ballooning with apical sparing (C: end-diastole, D: end-systole).

5.2 Echocardiography

Transthoracic echocardiography is the most important modality to distinguish this syndrome from AMI. It has many merits thanks to its non-invasiveness, portability, real-time accessibility, reproducibility and concurrent monitoring of anatomic and physiologic abnormalities (Lee, J.W. et al., 2011).

Echocardiography reveals the unique morphology of apical ballooning and the relative compensatory hypercontractility of the basal segments. One should closely observe two distinct features: (i) decrease in LVEF and (ii) (LVOT) obstruction. These factors are important to predict the severity and prognosis of stress-induced cardiomyopathy.

The decreased LVEF seen at hospital admission is a significant independent risk factor for death or cardiogenic shock (Lee, J.W. et al., 2010). The absence of recovery in left ventricular dysfunction within 1 week is also a powerful independent factor associated with mortality (Lee, P. H. et al., 2010).

Hypotensive events can be induced by dynamic LVOT obstruction, which results in the movement of the anterior mitral leaflets toward the interventricular septum in the systolic phase, so-called "systolic anterior motion" (SAM). Low cardiac output occurs as a result of reduced antegrade flow. This may occur in up to one-quarter of patients presenting with a septal bulge associated with SAM and mitral regurgitation (El Mahmoud et al., 2008). LVOT obstruction is a dynamic phenomenon depending on the hemodynamics at that time point, and thus echocardiography is a useful and readily accessible tool if unexplained hypotension or shock is observed.

Acute mitral regurgitation can be found in stress-induced cardiomyopathy. Mitral regurgitation seems to develop mainly due to displacement of the papillary muscle, which leads to impaired leaflet coaptation secondary to tethering. Parodi et al. suggested that mitral regurgitation accompanied by severe left ventricular dysfunction was a potent predictor of hemodynamic derangement leading to hazardous manifestations, including pulmonary edema and cardiogenic shock (Parodi et al., 2007).

Regional and global systolic function can be assessed and quantified by two-dimensional strain. This method is based on tracking the movement of stable acoustic patterns ("speckles") within the myocardium frame-by-frame throughout the cardiac cycle. Despite the general perception of basal hypercontractility, total longitudinal strain showed that systolic function in basal segments was decreased in one study (Heggemann et al., 2009).

Contrast echocardiography can be helpful in detection of the endocardial border (particularly if apical segments are difficult to evaluate because of poor image quality). Apical thrombus can be readily detected by contrast echocardiography. Contrast echocardiography can also demonstrate abnormalities in myocardial perfusion, which are indicative of microvascular dysfunction (Abdelmoneim, 2009). The normal myocardial perfusion pattern in the akinetic apex helps to discriminate stress-induced cardiomyopathy from anterior wall myocardial infarction.

Real-time three-dimensional imaging techniques and transesophageal echocardiography can give better information on volumetric change and anatomic abnormalities

5.3 CMR

CMR provides information on wall-motion abnormalities as well as myocardial viability. Contrast-enhanced CMR can identify myocardial inflammation through the presence of edema by T2-weighted images and/or myocardial tissue injury by late gadolinium

enhancement (Schmalfuss, 2011). The special morphological pattern of late gadolinium uptake was reported recently for the first time (Avegliano et al., 2011). Early CMR (within 72 h of hospital admission) demonstrated mild enhancement of signals in the segments with abnormal contractility, which was clearly different from the segments with no signal enhancement and normal contractility. This special morphological pattern corresponded to localized inflammation and edema in the affected area, which could be related to slower gadolinium washout determined by interstitial edema and inflammation (and perhaps very small areas of necrosis). This pattern becomes normal after recovery from myocardial edema and contractility. The morphological pattern suggests that the pathophysiology is related to diffuse damage of the myocardium and the microcirculation rather than involvement of coronary epicardial vessels.

5.4 Nuclear imaging

Single-photon emission computed tomography (SPECT) shows perfusion defects in the affected segment beyond single coronary distribution. Imaging also showed that the perfusion defect was slightly smaller in extent compared with the distribution of the wall-motion defect in one study (Skovgaard et al., 2010). Fluorine 18 fluorodeoxyglucose positron emission tomography in the acute phase showed reduced (but not absent) glucose uptake in almost the entire left ventricle, indicating viable tissue. The myocardial glucose uptake 3 months later was evenly distributed in the affected areas.

The findings of ^{123}I -meta-iodobenzylguanidine myocardial scintigraphy depicted a unique pattern of ventricular asynergy and suggested the existence of cardiac sympathetic hyperactivity (Akashi et al., 2004). Conversely, Skovgaard et al. could not find signs of cardiac sympathetic dysfunction as evidenced by a normal and unchanged washout rate (Skovgaard et al., 2010). However, they demonstrated the interesting finding of increased uptake in the lung, which was shown in chronic heart failure.

The findings from these nuclear imaging studies provide possible evidence of coronary microvascular dysfunction.

6. Mechanisms of stress-induced cardiomyopathy

The mechanisms of stress-induced cardiomyopathy are incompletely understood. However, a growing body of evidence could explain the possible mechanism and pathophysiology. A proposed mechanism of stress-induced cardiomyopathy is summarized in Fig. 2.

6.1 Brain–heart connection

Although the heart has an intrinsic capacity to maintain homeostasis, it is always ready to recognize extrinsic stimuli through brain–heart connections and can elicit an appropriate response for physiological demands. This protective process is called the "stress system". The main central effectors of the stress system are highly interconnected and include hypothalamic corticotropin-releasing hormone and locus ceruleus-derived norepinephrine (Chrousos, 2009, as cited in Charmandari et al., 2005 and Chrousos & Gold, 1992). The principal peripheral effectors are glucocorticoids, which are regulated by the hypothalamic–pituitary–adrenal axis, and the catecholamines norepinephrine and epinephrine, which are regulated by the systemic and adrenomedullary sympathetic nervous systems (Chrousos, 2009). A functional positive feedback loop is formed by hypothalamic corticotrophin-

releasing hormone and brainstem locus ceruleus-norepinephrine systems (Chrousos, 2007). The locus ceruleus also participates in a feedback loop with the adrenal medulla and the limbic system. The adrenal gland secretes epinephrine, which stimulates the locus ceruleus. Norepinephrine is released consecutively by this stimulus, which then sends signals to the hippocampus and amygdala. The latter can re-stimulate the locus ceruleus in sequence (Soufer, 2002).

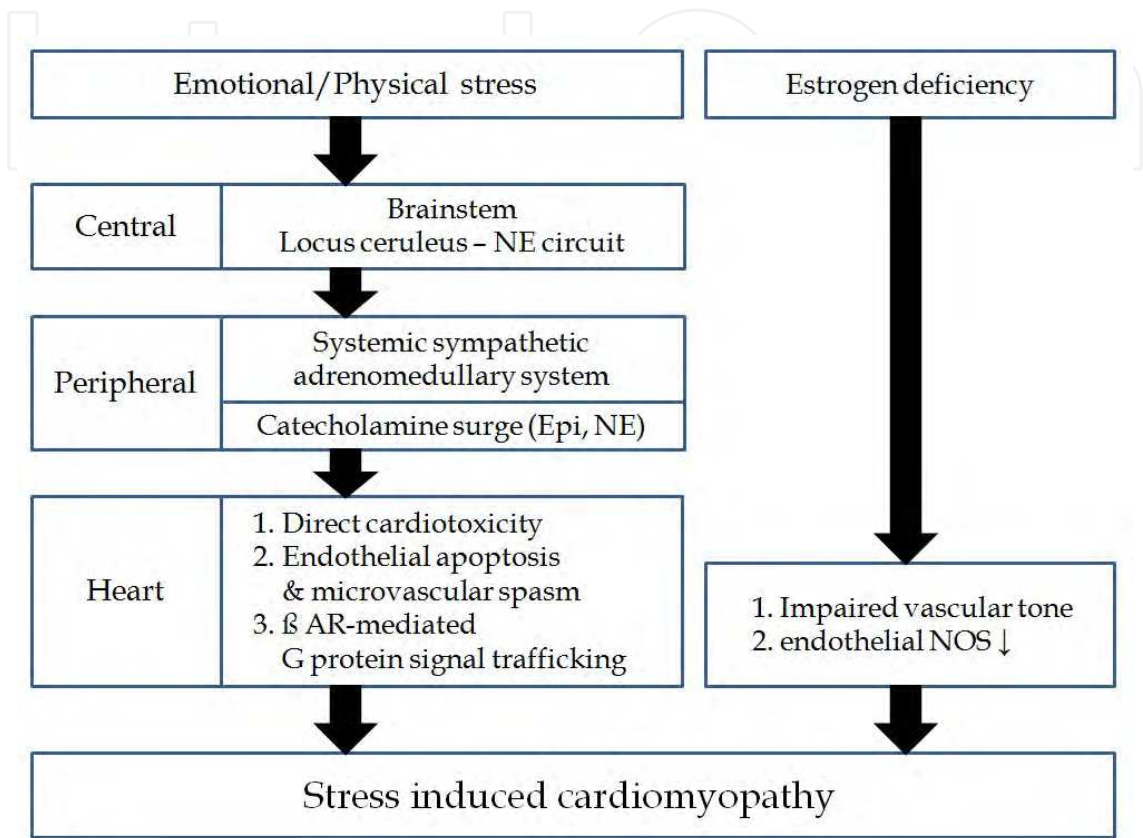


Fig. 2. Proposed mechanism of stress-induced cardiomyopathy. NE, norepinephrine; Epi, epinephrine; AR, adrenoreceptor; NOS, nitric oxide synthase.

Incessant emotional and/or physical stimuli may activate and sustain positive feedback stress response systems and result in marked elevation of plasma catecholamine levels in patients with stress-induced cardiomyopathy (Balkin & Cohen, 2011).

6.2 Catecholamine excess

Several situations that could induce sympathetic activation have suggested that cardiac dysfunction might be closely related to catecholamine excess. Subarachnoid hemorrhage and pheochromocytoma are typical examples (Kono et al., 1994; Pollick et al., 1988; Scott & Gutterman, 1995). Catecholamines could contribute to myocardial stunning in the absence of relevant myocardial perfusion abnormalities at rest (Morel et al., 2009). With respect to stress-induced cardiomyopathy, the possible contribution of catecholamines can be summarized into three components; (1) direct toxicity of norepinephrine/epinephrine and their metabolites; (2) adrenergic stimuli with spasm of the epicardial coronary artery and/or microvasculature; and (3) β -adrenoreceptor-mediated stimulus-dependent G-protein stimulus trafficking.

6.2.1 Catecholamine toxicity

Proof of direct catecholamine-induced cardiotoxicity has been known since the mid-1970s. Early investigations showed that intravenous injection catecholamines in rats could affect morphological change on the cardiomyocyte plasma membrane (the “sarcolemma”) (Balkin & Cohen, 2011, as cited in Rona et al., 1975 & Boutet et al., 1976). When they injected catecholamines, the extracellular macromolecular tracer horseradish peroxidase became localized to intracellular compartments, which was retained in the extracellular environment in a normal physiological state.

The synthetic catecholamine isoproterenol was shown to increase myocardial Ca^{2+} content and depress cardiac sarcolemmal ATP-dependent Ca^{2+} uptake, Ca^{2+} -stimulated ATPase activity and Na^{+} -dependent Ca^{2+} accumulation in experimental hearts (Tappia, 2001). Those authors also demonstrated that similar findings were seen in isolated rat hearts perfused with the catecholamine oxidation product adrenochrome, (10–25 $\mu\text{g}/\text{mL}$).

These findings suggested that catecholamine and the oxidative stress that they cause result in the development of intracellular Ca^{2+} overload, heart dysfunction and subsequent myocardial death.

6.2.2 Catecholamine and microvascular spasm

The $\alpha 1$ -adrenoreceptor is located in smooth muscle cells, which causes vasoconstriction in blood vessels (including the epicardial coronary artery). However, provocation tests using infusions of ergonovine or acetylcholine induced multivessel spasm in only 28% of patients with documented stress-induced cardiomyopathy (Gianni et al., 2006). This finding is insufficient to explain the underlying mechanism of stress-induced cardiomyopathy.

Microvascular spasm by catecholamine-induced sympathetic stimulation can alter the oxygen delivery of the myocardium, which develops localized contractile dysfunction within seconds. If blood flow is restored before myocardial damage, cardiac function can recover. This phenomenon is termed “stunned” or “hibernating” myocardium (Heusch & Schulz, 1996). It may take days or weeks for such cardiac dysfunction to recover.

As mentioned above, contrast echocardiographic perfusion imaging, CMR and nuclear imaging provide evidences of coronary microvascular dysfunction. Uchida et al. investigated the hypothesis that coronary microvessel apoptosis could be the missing link between stress and stress induced cardiomyopathy (Uchida et al., 2010). Plasma catecholamines, thrombolysis in myocardial infarction (TIMI) coronary flow grade and myocardial perfusion grade, and apoptosis of coronary microvessels in the biopsied myocardial specimens by terminal deoxynucleotidyl transferase-mediated nick end-labeling (TUNEL) were examined in 8 female patients with stress-induced cardiomyopathy. They found elevated levels of plasma epinephrine and norepinephrine, delayed myocardial perfusion without flow disturbance in the epicardial coronary arteries, focal myocardial necrosis, as well as extensive apoptosis of coronary microvessels in arterioles, venules and capillaries.

Reactive hyperemia as a parameter of endothelial function and vascular response to acute mental stress could be measured by peripheral arterial tonometry. Women with a history of stress-induced cardiomyopathy demonstrated impaired endothelium-dependent vasodilation, excessive vasoconstriction, and augmented sympathetic activation after experiencing acute mental stress compared with age-matched post-menopausal controls and patients with myocardial infarction (Martin et al., 2010).

In summary, it can be hypothesized that catecholamine-induced apoptosis of endothelial cells of coronary microvessels and the subsequent microvessel spasm which results in myocardial stunning by oxidative stress due to the ischemia-reperfusion mechanism leads to stress induced cardiomyopathy (Uchida et al., 2010).

6.2.3 β -adrenoreceptor-mediated stimulus-dependent G-protein stimulus trafficking

β -adrenoreceptors are members of one of the largest families of cell-surface signaling proteins called G-protein-coupled receptors (GPCRs). The main function of GPCRs is to convert extracellular stimuli into intracellular signals (Rosenbaum et al., 2009). Cardiac tissue has two subtypes of β -adrenoreceptor: β_1 and β_2 . The β_1 -adrenoreceptor stimulates only the G- α_s protein. However, the β_2 -adrenoreceptor can activate two G proteins, G- α_s and G- α_i (part of the Gs and Gi heterotrimers, respectively), which differentially regulate adenylate cyclase. The latter generates cyclic adenosine monophosphate (cAMP), which activates protein kinase A (PKA) (Rosenbaum et al., 2009).

Specifically, in the heart, PKA phosphorylates the proteins involved in energy metabolism and excitation-contraction coupling. These include glycogen phosphorylase kinase, the L-type calcium channel, the sarcoplasmic reticulum membrane protein phospholamban, and cytoskeletal proteins. These phosphorylation events result in enhanced cardiac contractility (inotropy), accelerated cardiac relaxation (lusitropy), and increased heart rate (chronotropy) (Balkin & Cohen, 2011, as cited in Xiao, 2001 & Bers, 2002).

At physiological and elevated concentrations, norepinephrine, released from the sympathetic nerves, acts predominantly via the β_1 -adrenoreceptor on ventricular cardiomyocytes, exerting positive inotropic and lusitropic responses. Epinephrine also binds the β_1 -adrenoreceptor, but has a higher affinity for the β_2 -adrenoreceptor. At physiological concentrations, epinephrine binding to the β_2 -adrenoreceptor activates the Gs protein. At higher "supraphysiological" concentrations, epinephrine binds to the β_2 -adrenoreceptor and switches signaling from the Gs protein to the Gi protein, a process called "stimulus trafficking". This process results in negative inotropy, negative lusitropy and negative chronotropy. After the surge of epinephrine has finished, the β_2 -adrenoreceptor coupled to Gi proteins switches back to Gs protein coupling or is internalized and degraded, enabling cardiomyocytes to recover their inotropic function (Lyon et al., 2008).

6.3 Estrogen deficiency

Studies have shown that post-menopausal women are susceptible to stress-induced cardiomyopathy (Bybee et al., 2004). This strong female predominance has been strongly associated with estrogen deficiency. Indeed, ovariectomised rats without estradiol supplementation exposed to immobilization stress had reduced left ventricular systolic function and increased heart rate and blood pressure in comparison with rats that were supplemented with estradiol (Ueyama et al., 2007). They also demonstrated that chronic supplementation with estrogen attenuated stress-induced sympatho-adrenal outflow from the brain to the heart (indirect action on the nervous system) and upregulated cardioprotective substances such as atrial natriuretic peptide and heat shock protein 70 in the heart (direct action on the heart).

Estrogen has direct and indirect cardioprotective effects. The direct effect is rapid vasodilation primarily by activation of endothelial nitric oxide synthase (eNOS). The indirect long-term effect involves changes in the genetic expression of proteins that regulate vascular tone and the response to injury (Mendelsohn, 2002).

7. Prognosis and treatment

In most cases, the prognosis of stress-induced cardiomyopathy is good. Reported overall in-hospital mortality is 1.1% (Gianni et al., 2006), but the range varies to ~15–16% (Sharkey et al., 2010, and Lee, P.H. et al., 2010). The prevalence of complications was ~20%, including cardiogenic shock, acute heart failure, arrhythmias, intraventricular thrombus formation associated with distal embolization, left ventricular free wall rupture, recurrence, and even death (Bybee et al., 2004; Gianni et al., 2006; Zeb et al., 2010).

Acute systolic heart failure is the most common complication of stress-induced cardiomyopathy, and occurs in ~45% of patients (Madhavan et al., 2011). Madhavan et al. developed and validated a risk score that can be calculated at the time of presentation. Scores of 1, 2, and 3 points were associated with a risk of acute heart failure of 28%, 58%, and 85%, respectively. No specific therapy is required but, if needed, diuretics are used to improve pulmonary edema. Combined α - & β -blockers may be advantageous, but the usefulness of these agents in combination should be evaluated in the future.

Cardiogenic shock may occur in the acute phase of stress-induced cardiomyopathy. Shock may be due to systolic dysfunction, or be secondary dynamic LVOT obstruction. Patients with systolic anterior motion or LVOT obstruction should not be exposed to inotropic agents even if there are in shock. Insertion of an intra-aortic balloon pump may be needed until the recovery of cardiac function is achieved.

Right ventricular involvement is relatively common and associated with lower LVEF, a longer duration of hospitalization, more complications (e.g., severe congestive heart failure), the use of an intra-aortic balloon pump, and cardiopulmonary resuscitation (Elesber et al., 2006). It has been reported that pleural effusion was more frequent in patients with stress-induced cardiomyopathy and was predictive of right ventricular dysfunction (Haghi et al., 2006).

One should keep in mind the possibility of intraventricular thrombus formation, which can be found not only in the left ventricle but also in the right ventricle and left atrial appendage (Buchholz et al., 2010; Haghi et al., 2008; Sharkey et al., 2010). Apical thrombus in the left ventricle carries a great risk of cerebrovascular accident and distal embolization during the recovery phase. Short-term use of anticoagulants and heparin as well as close follow-up echocardiography can protect against additional embolic events.

Arrhythmic complications include ventricular tachycardia, ventricular fibrillation, atrial fibrillation, atrioventricular block and sinus node dysfunction. The exact prevalence is unclear and no specific treatment has been developed. This issue needs more pooled data to assess the associations between stress-induced cardiomyopathy and arrhythmias (including conduction disorders).

The true prevalence of recurrence is not known, but only 3.5–5% of patients experienced recurrence in two studies (Gianni et al., 2006, and Sharkey et al., 2010).

Levosimendan has been suggested to be an ideal drug for patients with cardiogenic shock (Padayachee, 2007). Levosimendan is a non-catecholamine inotrope which sensitizes troponin C to calcium, leading to improved contractility. In addition, levosimendan does not compromise diastolic function. The opening of adenosine triphosphate-dependent potassium channels by levosimendan causes vasodilation. This decreases preload, afterload and pulmonary vascular resistance, and improves coronary perfusion. Further studies are required to determine the safety and efficacy of this agent before widespread use can be recommended.

8. Summary and conclusion

The development of stress-induced cardiomyopathy involves multiple interactions. Emotional and/or physical stressors activate the stress system via positive feedback loops and catecholamines are produced. Excessive amounts of catecholamines directly affect cardiomyocytes, induce apoptosis of endothelial cells of coronary microvessels with subsequent microvessel spasm and β -adrenoreceptor-mediated stimulus-dependent G-protein stimulus trafficking. Estrogen deficiency makes the heart to vulnerable to stressors. Depending on the severity of cardiac involvement, various presentations can be seen. Diagnostic modalities should be chosen according to specific situations. Echocardiography is essential to monitor recovery or possible complications, and to plan further treatment. A growing body of evidence promises better understanding of stress-induced cardiomyopathy.

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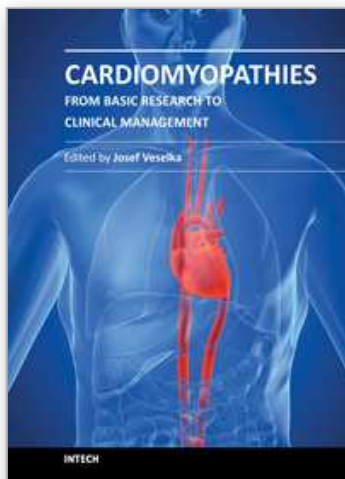
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Cardiomyopathy means "heart (cardio) muscle (myo) disease (pathy)". Currently, cardiomyopathies are defined as myocardial disorders in which the heart muscle is structurally and/or functionally abnormal in the absence of a coronary artery disease,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

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