REVIEW

Stress cardiomyopathy: aetiology and management

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Stress cardiomyopathy is a condition caused by intense emotional or physical stress leading to rapid and severe reversible cardiac dysfunction. It mimics myocardial infarction with changes in the electrocardiogram and echocardiogram, but without any obstructive coronary artery disease. Due to the awareness created by the media and internet, every patient is aware that they should seek help immediately for chest pain. Therefore physicians should be aware of this new condition and how to diagnose and treat it, even though the causal mechanisms are not yet fully understood.

Stress cardiomyopathy is a condition in which intense emotional or physical stress can cause rapid and severe heart muscle weakness. The pattern of left ventricular dysfunction was first described in Japan and has been referred to as “tako-tsubo cardiomyopathy”,¹ named after the fishing pot with a narrow neck and wide base that is used to trap octopus. “Tako-tsubo cardiomyopathy”, also known as “apical ballooning syndrome”, “apical cardiomyopathy”, “stress cardiomyopathy” or “broken-heart syndrome” is now increasingly recognised in other countries as well.^{2–3} “Transient left ventricular apical ballooning” has also been used to describe similar cardiac contractile function in patients after physical or emotional stress (fig 1).^{4–5}

This condition can occur following a variety of emotional stressors such as grief, fear, extreme anger, and surprise. On the other hand numerous physical stressors such as stroke, seizure or acute asthma can also trigger the condition. Common presenting signs of this syndrome are chest pain, ST segment elevation in the precordial leads, mild elevation of cardiac enzyme and biomarker levels, and transient apical systolic left ventricular dysfunction in the absence of obstructive epicardial coronary disease.^{4–5}

CLINICAL FEATURES

Most of the patients with stress cardiomyopathy usually present with severe chest pain, dyspnoea, or both during emotional stress.⁶ The pain could be misleading as it resembles that of acute myocardial infarction in its nature (heavy, squeezing and crushing) and site (central portion of the chest and/or the epigastrium, occasionally radiating to the arms), causing anxiety. It can also simulate pain of acute pericarditis, pulmonary embolism, acute aortic dissection and costochondritis, as all these mimic acute myocardial infarction. Therefore all these conditions should be excluded through investigations including coronary angiogram to

identify any significant blockages that would cause the left ventricular dysfunction.

Coronary vasospasm can lead to life-threatening cardiac arrhythmias in patients without any haemodynamically significant coronary artery disease like stress cardiomyopathy.⁸ It can cause arrhythmias due to QT prolongation and is also reported to be associated with torsade de pointes.^{9–10} In the absence of critical coronary arterial disease, the diagnosis of stress cardiomyopathy should be considered when the history reveals that the cardiac symptoms were precipitated by intense emotional stress. Echocardiography reveals a unique pattern of left ventricular dysfunction characterised by apical and mid-ventricular contractile abnormalities with sparing of the basal segments.⁶ Most of these patients have a complete recovery without any complications. There can be various electrocardiographic (ECG) and echocardiographic findings in stress cardiomyopathy (boxes 1 and 2).

AETIOLOGY

Emotional stress can precipitate severe, reversible, left ventricular dysfunction in patients without coronary disease. Box 3 summarises various mechanisms postulated in relation to stress cardiomyopathy. Even though the mechanisms underlying stress cardiomyopathy are unclear, exaggerated sympathetic stimulation is probably central to its causation. Catecholamine excess has been implicated; nevertheless the association between the two is unknown. One possibility is ischaemia resulting from epicardial coronary arterial spasm. Increased sympathetic tone can lead to vasoconstriction in patients without coronary disease.¹¹ Multivessel epicardial coronary artery spasm has been reported, but microvascular spasm has also been suggested. Others have demonstrated reduced coronary flow reserve and regional defects on cardiac imaging in such patients,¹² suggesting the presence of sympathetically mediated microcirculatory dysfunction.

Another possible mechanism of catecholamine-mediated myocardial stunning is direct myocyte injury. Adrenoceptor density is higher in the apex, compared to other areas of the myocardium.⁶ Elevated catecholamine levels result in a concentration-dependent decrease in myocyte viability, as demonstrated by a significant release of creatine kinase from cells and hence a decrease in the viability through cyclic AMP-mediated calcium overload.¹³ Animal models have demonstrated that catecholamines are a potential source of free radicals, which by promoting lipid peroxidation

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Abbreviations: ACE, angiotensin-converting enzyme; AMI, acute myocardial infarction; ECG, electrocardiogram; MIBG, metaiodobenzyl guanidine

Figure 1 Ventriculographic assessment of cardiac function and magnetic resonance imaging (MRI) assessment of myocardial viability at admission in a patient with stress cardiomyopathy.⁶ Contrast-enhanced ventriculography during diastole (panel A) and systole (panel B) demonstrates apical and mid-ventricular akinesis, with relative sparing of the base of the heart (arrow). In panel C, MRI in the long-axis view reveals that the akinetic regions seen on ventriculography are dark and hypoenhanced, consistent with the presence of viable myocardium. Panel D, which is presented for purposes of comparison, shows hyperenhancement (arrow), indicative of necrosis and decreased viability, after an acute anterior myocardial infarction. Reproduced with permission from Massachusetts Medical Society.

may increase membrane permeability and myocyte injury leading to cardiomyopathy.¹⁴ Myocyte dysfunction can occur through increased transsarcolemmal calcium influx and cellular calcium overload due to the ability of the free radicals to interfere with sodium and calcium transporters.¹⁵

Abnormal coronary flow in the absence of obstructive disease has recently been reported in patients with stress-related myocardial dysfunction.¹⁶ ¹²³I-MIBG (metaiodobenzyl guanidine) myocardial scintigraphy showed a unique pattern of ventricular asynergy suggesting the existence of cardiac sympathetic hyperactivity with maintained coronary blood flow. This implies that stress cardiomyopathy might have been caused by neurogenic myocardial stunning.¹⁷

An angiographic study of patients with stress cardiomyopathy by Kurisu *et al*¹ showed that 70% had coronary spasm in response to provocative manoeuvres, and electrocardiographic evidence of ST segment elevation was common at presentation (box 1). To the contrary, another study by Wittstein *et al*⁶ demonstrated no angiographic evidence of epicardial spasm, and ST segment elevation was seen rarely. According to the latter study, patients did initially have contractile abnormalities in multiple vascular territories, but multivessel epicardial spasm as an explanation for this finding seemed unlikely, given the relative absence of ST segment elevation and minimal enzymatic evidence of myocardial necrosis. The distribution of primary cardiac insult does not

correspond to the perfusion territory of a single coronary artery, and there is myocardial stunning rather than infarction.

Patients usually have supra-physiological levels of plasma catecholamines and stress-related neuropeptides. Unlike polymorphonuclear inflammation seen with infarction, in stress cardiomyopathy there is contraction band necrosis, a unique form of myocyte injury characterised by hypercontracted sarcomeres, dense eosinophilic transverse bands, and an interstitial mononuclear inflammatory response. Endomyocardial biopsy demonstrated the presence of contraction band necrosis in patients with this syndrome.⁶ Contraction band necrosis is a type of cell death identified as early as 2 mins after cell injury has occurred and can cause release of cardiac enzymes.¹⁸ Focal myocarditis and contraction band necrosis has been found in states of excess circulating catecholamine-like pheochromocytoma,¹⁹ subarachnoid haemorrhage,^{20, 21} eclampsia²¹ and in people who died of fatal asthma.²² It has also been documented in autopsies of patients with normal coronary vessels who suffered from coronary spasm due to various causes.^{21, 23} These suggest that catecholamines may be a link between emotional stress and cardiac injury.

WHO ARE PRONE TO STRESS CARDIOMYOPATHY?

From the available medical literature so far, women—especially middle aged or elderly—are the most commonly affected. While it can also occur in young women and men, the vast majority of these patients are post-menopausal women.^{24, 25} Indeed, more than 90% of patients suffering from stress cardiomyopathy are females.²⁶ The basis for this predisposition is unknown. Sex hormones exert important influences on the sympathetic neurohormonal axis²⁷ as well as on coronary vasoreactivity,²⁸ but sex-related differences in catecholamine metabolism and responsiveness are complex and remain poorly understood. Reversible myocardial dysfunction can develop in critically ill patients without any primary heart disease.²⁹ This syndrome is associated with systolic dysfunction, segmental contractile disturbance and electrocardiographic changes.

Box 1 Electrocardiographic (ECG) findings^{6, 7}

Myocardial stunning may present as the following changes in ECG (fig 2):

- Diffuse symmetric T-wave inversion
- Pronounced prolongation of the QT interval
- Loss of R wave progression
- Prolonged PR interval
- Pathologic Q waves in leads V1, V2, V3 and aVL

Box 2 Echocardiographic findings

- Apical akinesis or dyskinesis
- Reduced left ventricular ejection fraction and systolic dysfunction
- Apical ballooning with abnormal wall motion of the mid and distal left ventricle
- Restoration of normal myocardial function with time

Methods to predict who will develop myocardial stunning would be very helpful. Serum catecholamine levels might be expected to reasonably coincide with the catecholamine surge and myocardial stunning; however, the available data have not borne this out.³⁰ Cardiac troponins can be used as a screening test for predicting myocardial stunning.³¹ Although troponin is helpful, it does not answer several important questions: Why do some patients have an elevation in troponin and not others? What are the underlying mechanisms that lead to myocardial stunning? Genotyping was done for catecholamine receptor subtypes.³² Several genetic receptor subtypes were associated with both troponin release and depressed ejection fraction on echocardiography. This implicates the genetic code of receptor subtypes, and probably receptor function, in troponin release and myocardial stunning.

MANAGEMENT

The management of stress cardiomyopathy mainly consists of supportive and symptomatic treatment.³³ We should be able to exclude any significant coronary artery disease.³⁴ Initially patients are managed as for myocardial infarction, including urgent coronary angiography with a view to primary coronary intervention. As is the case for patients with coronary artery disease, all patients should be started on aspirin, low molecular weight heparins, and angiotensin-converting enzyme (ACE) inhibitors; β -blockers and diuretics can be started if needed. Beyond the standard supportive care for congestive heart failure with diuretics and vasodilators, the treatment of stress cardiomyopathy largely remains empirical. With good initial medical support, patients with stress cardiomyopathy show good clinical and echocardiographic improvement (fig 3). They also have an excellent prognosis.

Patients should be monitored for the development of arrhythmias, heart failure and mechanical complications. Patients can have acute haemodynamic compromise and require vasopressor agents and intra-aortic balloon counterpulsation.⁷ Apical thrombus can form for which short-term anticoagulation may be

Box 3 Mechanisms of myocardial stunning

- Exaggerated sympathetic stimulation
- Ischaemia resulting from epicardial coronary arterial spasm
- Direct injury of myocytes by catecholamines
- Sympathetically mediated microcirculatory dysfunction

needed.^{26–35} Almost all patients who had left ventricular impairment return to normal within few weeks, and there are no reports concerning the proportion of patients left with significant long term left ventricular impairment.^{36–37} The evolution, although mainly uneventful, can be complicated, rarely, by left ventricular rupture, thus making stress cardiomyopathy a newly recognised cause of sudden death in up to 3% of patients.^{26–33} Most of the patients will have normalised ejection fraction with restoration to previous functional cardiovascular status within 6 ± 3 days. This syndrome may recur in up to 10% of patients, making it difficult to know how long to continue treatment.⁷

Figure 3 Serial echocardiographic assessment of the ejection fraction in 19 patients with stress cardiomyopathy.⁶ Echocardiography was performed on admission; on hospital day 3, 4, 5, 6, or 7 (median, day 4); and at outpatient follow-up (a median of 21 days after the onset of symptoms). Gray lines illustrate values for individual patients. The black bar represents the median ejection fraction at each time; error bars show the interquartile range. $p < 0.001$ for the comparison between admission and inpatient values, and $p < 0.001$ for the comparisons between admission and outpatient values and between inpatient and outpatient values. Reproduced with permission from Massachusetts Medical Society.

A Patient 4

B Patient 2

C Patient 16

D Patient 18

Figure 2 Typical ECGs obtained 24–48 h after presentation in four patients with stress cardiomyopathy.⁶ Pronounced prolongation of the QT interval and diffuse symmetric T wave inversion are present in all four ECGs. Loss of R wave progression in leads V1, V2, and V3 is also evident in panels C and D. Reproduced with permission from Massachusetts Medical society.

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CONCLUSIONS

With available studies, it could be concluded that “Stress cardiomyopathy is a reversible dysfunction of the myocardium due to significant physical or psychological stresses”. There are a lot of uncertainties about stress cardiomyopathy. Why is it more common in women? It was initially reported only in Japan but now it is widely described in other countries as well. A definitive mechanism of myocardial stunning is still unknown and therefore further research on this subject will be required for the complete understanding of the pathogenesis of this syndrome.

MULTIPLE CHOICE QUESTIONS (TRUE (T)/FALSE (F); ANSWERS AFTER THE REFERENCES)

Which of the following statements are true?

- Most patients with stress cardiomyopathy present as acute myocardial infarction
- Stress cardiomyopathy mainly affects males who are subject to stress
- Adrenoceptor density is highest at the apex than in other areas of the myocardium
- Vasoconstriction in patients without coronary artery disease can be caused by increased sympathetic tone
- Even with good initial medical support, patients with stress cardiomyopathy do not show any clinical or echocardiographic improvement

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ANSWERS

(A) T (B) F (C) T (D) T (E) F