Takotsubo cardiomyopathy

How can an earthquake cause cardiogenic shock? Can a bereft lover really die from a broken heart? Takotsubo cardiomyopathy is an intriguing reversible condition which still mystifies and excites the layman and physician alike. This article explores the clinical essentials for recognizing and managing this group of complex patients.

Takotsubo cardiomyopathy is an increasingly recognized, but still underdiagnosed, cause of reversible acute cardiomyopathy. Takotsubo cardiomyopathy was first described in Japan, and named takotsubo after the left ventricle's resemblance to the Japanese fisherman's octopus trap at ventriculography (Sato et al, 1990). Also known as stress cardiomyopathy or 'broken heart syndrome', it is a clinical syndrome mimicking acute ST elevation myocardial infarction, but in the absence of causative obstructive coronary artery disease. Takotsubo cardiomyopathy is usually triggered by an event causing marked sympathetic surge with catecholamine release that induces a characteristic pattern of left ventricular wall motion abnormalities with systolic dysfunction. These changes typically resolve completely, at least macroscopically, in a period of days to weeks, depending on the severity of the acute abnormalities. The American Heart Association has classified takotsubo cardiomyopathy as a primary acquired cardiomyopathy (Maron et al, 2006), and diagnostic criteria have been proposed by both the Mayo Clinic (Prasad et al, 2008) and a Swedish group (Omerovic, 2011), although neither are universally accepted (*Table 1*).

Table 1. Modified Mayo clinic and Gothenburg criteria for diagnosis of takotsubo cardiomyopathy

Modified Mayo clinic criteria: all four required for diagnosis	Gothenburg criteria: all three required for diagnosis
A Transient hypokinesis, akinesis or dyskinesis in the left and/or right ventricular mid segments with or without apical involvement; regional wall motion abnormalities that extend beyond a single epicardial vascular distribution and frequently, but not always, a stressful trigger	1 Transient hypokinesis, akinesis or dyskinesis in the left and/or right ventricular segments and frequently, but not always, a stressful trigger (psychological or physical)
B The absence of obstructive coronary disease or angiographic evidence of acute plaque rupture	2 The absence of other pathological conditions (e.g. ischaemia, myocarditis, toxic damage, tachycardia) that may more credibly explain the regional dysfunction
C New electrocardiogram abnormalities (ST segment elevation and/or T wave inversion) or modest elevation in cardiac troponin	3 No elevation or modest elevation in cardiac troponin (i.e. disparity between the troponin level and the amount of the dysfunctional myocardium present)
D The absence of phaeochromocytoma and myocarditis	

See Prasad et al (2008); Omerovic (2011)

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Epidemiology

The incidence of takotsubo cardiomyopathy is almost certainly underestimated, but with increasing awareness and more widespread access to early coronary angiography it is now recognized more frequently. Several series in Asian and western, predominantly Caucasian, populations suggest around 1–2% of patients with suspected acute coronary syndrome are eventually diagnosed with takotsubo cardiomyopathy (Gianni et al, 2006; Kurowski et al, 2007). In the UK this equates to approximately 3000 cases per annum. The distribution is skewed such that postmenopausal women account for 70–90% of reported cases (Deshmukh et al, 2012; Schultz et al, 2012). Unlike acute coronary syndrome and other atherosclerosis-related conditions, presentation is more common in the summer months (Citro et al, 2009), and lacks the early morning peak associated with plaque rupture events (Sharkey et al, 2012).

Clinical presentation

The initial presentation of takotsubo cardiomyopathy resembles that of acute coronary syndrome, most commonly with acute chest pain (67.8%) and/or dyspnoea (17.8%), and sometimes with ventricular arrhythmia or cardiogenic shock (1.5% and 4.2% respectively). Typically there is a history of a recent emotional event (26.8%, e.g. bereavement, major argument, gambling losses), physical stress (37.8%, e.g. exhausting work, asthma attack, neuromuscular crisis), or a combination (e.g. suicide attempt), although in a significant minority no preceding stressor can be identified (34.3%; Gianni et al, 2006). Iatrogenic causes are also recognized, including induction of general anaesthetic, adrenaline administration and dobutamine stress echocardiography (Abraham et al, 2009). From a medicolegal perspective, there is

suspicion that physical restraint or electrical stunning (e.g. Taser weapons) might also trigger the condition (Cevik et al, 2009; Otahbachi et al, 2010).

In the emergency department, suspicion could be raised by description of symptoms typical for acute coronary syndrome in the context of a precipitating stressful event, particularly in postmenopausal women. Clinically, patients show signs of sympathetic overdrive with profound sweatiness, hypertension and anxiety.

Investigations

The different modalities of investigation are targeted towards rapid and precise distinction of takotsubo cardiomyopathy from ST elevation myocardial infarction, and subsequent determination of severity.

Electrocardiogram

The electrocardiogram is invariably abnormal in the ST and T wave segments.

ST segment elevation is present in 80% of cases which appears early in the presentation and is greatest in the precordial leads (Gianni et al, 2006). This then resolves leaving a negative T wave pattern that deepens progressively over the first few days (Kurisu et al, 2004). The changes are widespread, involving multiple coronary artery territories, and raising suspicion of myo- or pericarditis.

There is transient QTc prolongation which resolves to normal during the recovery phase. This is often very pronounced (>500 ms), which would rarely be seen in ST elevation myocardial infarction resulting from coronary occlusion, and increases the risk for arrhythmias (in particular torsades de pointes). The QTc can return quickly to normal (Kurisu et al, 2004), and this emphasizes the need for early imaging to identify the structural abnormalities before they resolve, in turn avoiding mistaken diagnosis of inherited long QT syndrome and unnecessary therapy such as defibrillator implantation.

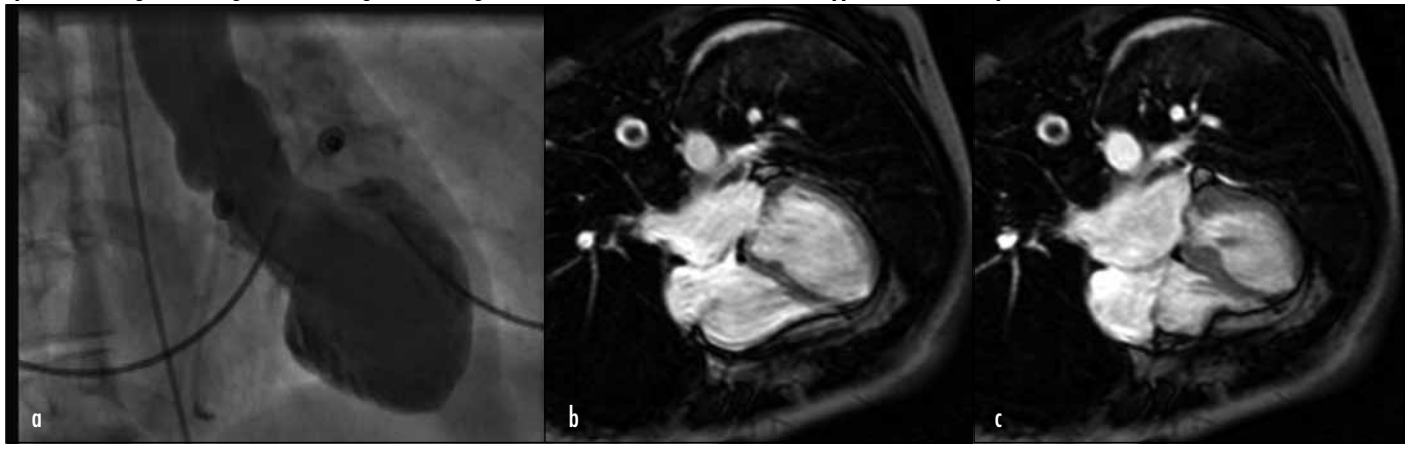
Differences between the electrocardiogram patterns seen in takotsubo cardiomyopathy and ST elevation myocardial infarction have been proposed as a tool for early triage, with the presence of ST segment depression in lead aVR alongside absence of ST segment elevation in lead V1 identifying takotsubo cardiomyopathy with 91% sensitivity and 96% specificity in one series of Asian patients (Kosuge et al, 2010), although this has not been replicated in Caucasian populations. In practice this would not preclude the need for cardiac catheterization in the context of acute chest pain with new ST segment elevation.

Cardiac catheterization

Most takotsubo cardiomyopathy patients will have urgent coronary angiography to exclude ST elevation myocardial infarction. In takotsubo cardiomyopathy the epicardial coronary arteries are typically normal, although bystander atherosclerotic coronary artery disease can be present. This is incidental to the index presentation and insufficient to cause the degree or pattern of left ventricular dysfunction. In one cohort of Japanese patients with takotsubo cardiomyopathy, 10% had coronary artery disease judged incidental to the primary diagnosis of takotsubo cardiomyopathy (Kurisu et al, 2009). Even in the presence of coronary artery atherosclerosis, intravascular ultrasound has demonstrated that plaque rupture or intracoronary thrombosis is not seen (Haghi et al, 2010). Once causative coronary occlusion has been excluded, ventriculography should be performed (unless contraindicated), and in takotsubo cardiomyopathy will often be diagnostic (*Figure 1*).

The typical pattern of wall motion abnormality is the apical and mid-wall hypokinesis that earned takotsubo cardiomyopathy its original description. Atypical variants may occur (see below). After diagnostic cardiac catheterization, early access to high quality cardiac imaging is

Figure 1. A 58-year-old woman presented to hospital with chest pain, dyspnoea and vomiting after being bullied at work. Her electrocardiogram showed widespread ST segment elevation. She underwent urgent cardiac catheterization which showed normal coronary arteries. a. Her ventriculogram showed marked hypokinesis at the apex, strongly suggestive of takotsubo cardiomyopathy. The diagnosis was confirmed on cardiac magnetic resonance imaging the same day. The absence of late gadolinium enhancement completely excluded myocardial infarction. Pictured here are four-chamber views at (b) end-diastole and (c) end-systole showing shortening and thickening of basal segments of the left ventricle, but severe hypokinesis at the apex.



essential, in particular echocardiography and, where available, cardiovascular magnetic resonance imaging.

Echocardiography

Echocardiography is readily available and aids diagnostic confirmation. Markedly reduced left ventricular systolic function is the most prominent feature, alongside the characteristic pattern of wall motion abnormality, with the left ventricular apex typically akinetic or markedly hypokinetic, and corresponding hypercontractility of the base. However, patients in the acute phase can have normal or near normal stroke volume with preserved cardiac output (Schultz et al, 2012). Assessment for left ventricular outflow tract obstruction is important in the presence of hypotension as this has important implications for further management. Contrast echocardiography may be helpful to exclude thrombosis in the akinetic left ventricular apex.

Cardiovascular magnetic resonance

Acute cardiovascular magnetic resonance imaging in takotsubo cardiomyopathy patients demonstrates four principal abnormalities (Eitel et al, 2011):

1. There is left ventricular hypokinesis with varying degrees of left ventricular dysfunction (*Figure 1*). One cardiovascular magnetic resonance series reported the classic pattern of apical hypokinesis in 82% of cases, with atypical midventricular (17%) and basal (1%) patterns (each with apical sparing) less frequently seen. Biventricular involvement (34%) may occur, and tends to be associated with more severe disease.
2. After infusion of the contrast agent gadolinium, the early phase scan will delineate left ventricular apical thrombus if present.
3. The delayed phase scan will demonstrate absence of the intense subendocardial to transmural pattern of late gadolinium enhancement that is typical of myocardial infarction. Patchy late gadolinium enhancement during the acute phase has been reported but is absent at follow up (Naruse et al, 2012). In a subgroup of patients a pattern of small, transmural late gadolinium enhancement persists, and is observed in the ventricular apex at follow up. In the absence of coronary atherosclerosis, and with the original hypokinesis during the acute phase involving a much wider volume of myocardium, this is not a conventional myocardial infarction. This may reflect pressure-induced ischaemia and myocardial necrosis caused by the extremely high intraventricular pressures which can be generated during acute stress, with the thin-walled apex most susceptible, although postmortem histological confirmation of this late gadolinium enhancement pattern is lacking.
4. Finally, T2-weighted studies can show increased regional water content, probably as a result of myocardial inflammation, typically collocated with the areas of left ventricular dysfunction, although this is less specific for takotsubo cardiomyopathy. In most cases all these abnormalities will have resolved at follow-up scanning at 2 months.

In those patients with suspected ST elevation myocardial infarction but normal coronaries, cardiovascular magnetic resonance's ability to show characteristics of the myocardial tissues provides an excellent technique for further assessment and differentiation of takotsubo cardiomyopathy from other acute heart failure syndromes such as acute myocarditis (Monney et al, 2011). In addition its ability to reliably exclude myocardial infarction, through analysis of distribution of wall motion abnormalities as well as with late gadolinium enhancement, has important implications for the individual patients and the health economy in removing the need for long-term secondary prevention of atherosclerosis. Its weakness is limited availability outside large centres, and a time lapse from presentation to scanning may allow some abnormalities to resolve before being fully appreciated.

Biomarkers

Serum assays of cardiac troponins, myoglobin, creatine kinase-MB (CK-MB), natriuretic peptides (BNP and NT-proBNP) can be, and usually are, all elevated in takotsubo cardiomyopathy, but none is sufficiently specific for diagnostic purposes. In most cases, a patient with takotsubo cardiomyopathy will have a dramatically elevated BNP alongside a marginally elevated troponin, reverse to the biomarker profile typically observed in ST elevation myocardial infarction (Madhavan et al, 2009). Ratios of different biomarkers at presentation could help differentiate takotsubo cardiomyopathy from ST elevation myocardial infarction (Fröhlich et al, 2012), although this needs to be further validated. For prognostication, marked or persistent elevation in NT-proBNP or BNP levels carries worse prognosis and correlates with the extent of catecholamine release, and severity of left ventricular dysfunction (Nguyen et al, 2011).

Acute cardiac complications

Takotsubo cardiomyopathy patients are a heterogenous group, and as such there is a spectrum of disease severity in takotsubo cardiomyopathy. Mild cases may exhibit only a minimal degree of left ventricular dysfunction and resolve quickly, while more severe cases presenting with cardiogenic shock make a more protracted recovery. In this latter group there are several factors contributing to the abrupt loss of cardiac output. The akinesis of the left ventricular apex causes an acute left ventricular systolic impairment, which results in marked reduction of ventricular ejection. With this, the hyperdynamic contraction in the base of the left ventricle may cause acute left ventricular outflow tract obstruction, sometimes associated with systolic anterior motion of the mitral valve and acute mitral regurgitation that may exacerbate the haemo-

dynamic abnormality and pulmonary congestion (Villareal et al, 2001; Fefer et al, 2009). These factors together can cause a severe acute pump failure and the clinical cardiogenic shock.

Other problems include complete atrioventricular block, which may require temporary pacing, but will usually resolve quickly in parallel to the functional recovery (Chadha et al, 2012); cardiac rupture, usually fatal without urgent surgery, which is more common in older hypertensive females (Kumar et al, 2011); and torsades de pointes or other ventricular tachyarrhythmias. Importantly, the apical wall motion abnormality predisposes to formation of thrombus within the left ventricular cavity (2% of cases in one cardiovascular magnetic resonance study; Eitel et al, 2011), and systemic embolic events (3%; Schultz et al, 2012) can be encountered.

Management

The central tenet of takotsubo cardiomyopathy is that ultimately the myocardial function will return to normal, and so the priority lies with aggressive supportive care to sustain life and minimize complications until full recovery is achieved. In mild cases, no treatment or a short course of medical therapy may be sufficient; in severe cases, consideration of mechanical support as a 'bridge to recovery' may be necessary. Takotsubo cardiomyopathy is a recently recognized entity and so there is still little evidence on which to base management rationale. This discussion is based on available evidence, current consensus, and the viewpoint of the authors.

Diagnosis and initial management

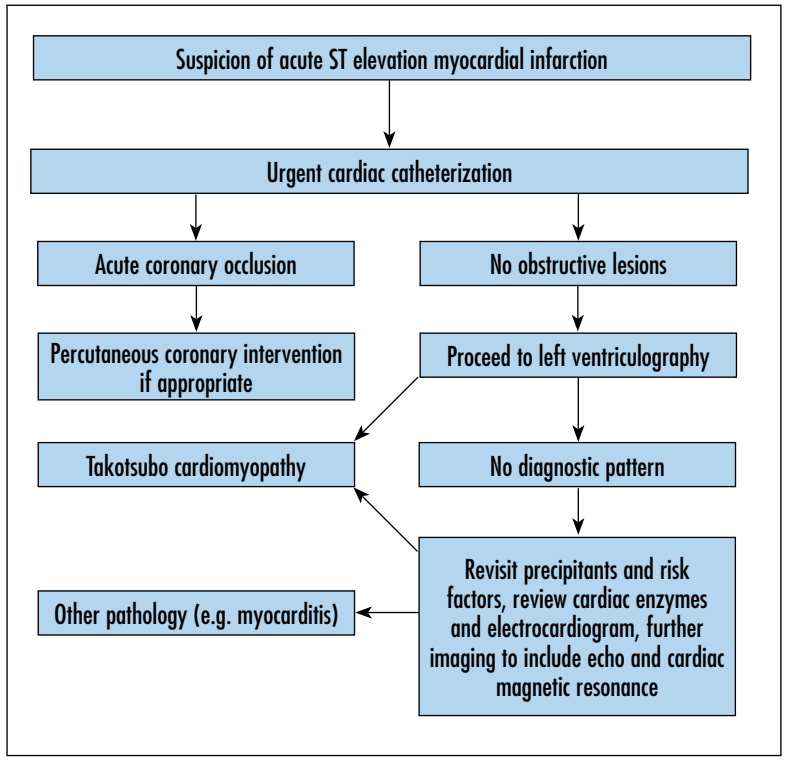
In the initial phase, standard protocols for management of ST elevation myocardial infarction should be followed until this has been excluded with cardiac catheterization confirming no culprit coronary lesions (*Figure 2*). Ventriculography at the time of coronary angiography is essential and often diagnostic in takotsubo cardiomyopathy, and an early complete echocardiogram will demonstrate the left ventricular dysfunction and characteristic pattern of wall motion abnormality (*Figure 1*). In some patients left ventricular function may normalize within 2–3 hours (authors' unpublished observations) which strengthens the need for the early assessment of left ventricular function.

Patients should be admitted to an acute cardiac or medical unit with continuous cardiac electrocardiogram monitoring given the acute risk of arrhythmias, particularly in the setting of significantly prolonged QTc interval. The authors would advise that monitoring continues until the QTc interval has returned to a level considered low risk for sudden cardiac death. Non-invasive monitoring of haemodynamic parameters such as cardiac output, stroke volume and peripheral vascular resistance, for example with impedance electrocardiography, may be helpful in continuous assessment of the patient's stability, and for evaluation of the haemodynamic consequences of pharmacological treatment. Contrast echocardiography and cardiovascular magnetic resonance in the early phase post-gadolinium will exclude left ventricular thrombus, and the late post-gadolinium phase will provide further evidence to exclude myocardial infarction. Once excluded, antiplatelet and anticholesterol drugs can be reviewed for discontinuation. Systemic anticoagulation should be initiated if left ventricular thrombus is confirmed.

Mild cases

Mild cases with rapid symptomatic improvement may deserve no therapy and early discharge. Patients with persistent symptoms and left ventricular dysfunction often warrant conventional heart failure therapy with graded introduction of angiotensin-converting enzyme inhibitors and beta-blockers licensed for heart failure. However, there is evidence that some takotsubo cardiomyopathy patients can have altered peripheral sympathetic nerve activity associated with low peripheral vascular resistance, and if peripheral vascular resistance is demonstrated to be significantly reduced then angiotensin-converting enzyme inhibitors may be withheld. There is no clinical evidence for superiority of one specific drug over another, although studies in a novel animal model in the authors' laboratory have suggested carvedilol may have a beneficial effect above other beta-blockers (Paur et al, 2012). Beta-blockers may also reduce the risk of cardiac rupture (Kumar et al, 2011).

Figure 2. Diagnostic management algorithm for patients with suspected takotsubo cardiomyopathy.

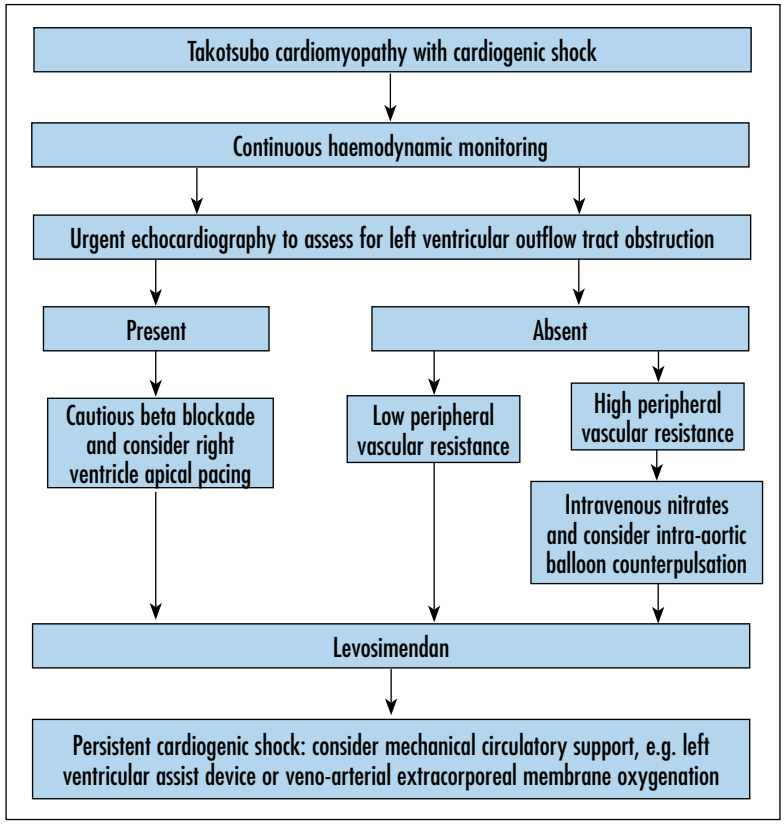


Severe cases with cardiogenic shock

Takotsubo cardiomyopathy with severe haemodynamic instability provides unique challenges. Urgent echocardiographic assessment is essential both to establish the degree of left ventricular systolic impairment and crucially to define the presence or absence of dynamic left ventricular outflow tract obstruction (which may have already been identified at cardiac catheterization by pull-back across the aortic valve). If left ventricular outflow tract obstruction is identified, beta-blockers should be cautiously introduced to prolong diastolic filling time and increase in left ventricular end-diastolic volume, reducing the left ventricular outflow tract gradient and improving cardiac output (Fefer et al, 2009), and electrical pacing of the right ventricular apex could be considered. In this situation, and in cases where the low cardiac output is associated with low peripheral vascular resistance, afterload reduction with intravenous nitrates and angiotensin-converting enzyme inhibitors can be detrimental and should be avoided (*Figure 3*).

Intra-aortic balloon counterpulsation has haemodynamic benefit largely through afterload reduction in the systolic phase and improved coronary perfusion in the diastolic phase. Theoretically it avoids complications of positive inotropy such as increased myocardial oxygen demand, although absolute benefit in patients with normal coronary arteries will be less than for those patients with cardiogenic shock in the context of myocardial infarction. Patient selection is critical if considering intra-aortic balloon counterpulsation, especially in light of recent neutral data from the IABP-SHOCK II trial (Thiele et al, 2012), and given the theoretical risk (never described clinically in takotsubo cardiomyopathy) that intra-aortic balloon counterpulsation and afterload reduction could worsen dynamic left ventricular outflow tract obstruction.

Figure 3. Management algorithm for patients with confirmed takotsubo cardiomyopathy complicated by cardiogenic shock.



The decision to use sympathomimetic drugs for positive inotropy is challenging and counterintuitive in takotsubo cardiomyopathy. Given its aetiology, further activation of catecholamine receptors or their downstream molecular pathways might worsen the left ventricular dysfunction. In addition dobutamine infusion may worsen dynamic left ventricular outflow tract obstruction, and many cases of dobutamine-induced takotsubo cardiomyopathy have been described during stress protocols (e.g. Abraham et al, 2009). In contrast, levosimendan is a positive inotrope that acts to sensitize cardiac myofilaments to calcium and, in an animal model of takotsubo cardiomyopathy, levosimendan was shown to be effective rescue from cardiogenic shock (Paur et al, 2012). Although further studies are necessary to define its role, levosimendan is the authors' recommendation for inotropic drug therapy in takotsubo cardiomyopathy with cardiogenic shock. However, given its limited availability, medical practitioners may be forced to resort to alternatives (e.g. noradrenaline) as the only available inotrope until transfer to a tertiary centre.

In patients with refractory cardiogenic shock and deteriorating multiorgan failure, it is appropriate to consider early referral for veno-arterial extracorporeal membrane oxygenation or for implantation of a left or biventricular assist device as a 'bridge to recovery', given the ventricular function of these patients has an excellent chance of full recovery (Redfors et al, 2012; *Figure 3*).

In the recovery phase, it is appropriate to introduce standard heart failure therapy as haemodynamics allow including angiotensin-converting enzyme inhibitors, beta-blockers and potentially an aldosterone receptor antagonist.

Other considerations

Takotsubo cardiomyopathy can be the herald for an underlying medical condition such as phaeochromocytoma or intracranial pathologies, and consideration should be given to appropriate screening especially if the patient is young, male or has an atypical pattern of wall motion abnormality (Cesaretti et al, 2010). Complete explanation of the diagnosis to the patient and appropriate communication with GP is essential. Patients must be aware that they have not suffered a 'heart attack' and their GP must be clear that – in the absence of comorbidities that would mandate it – there is no evidence to support long-term secondary prevention therapies started during an acute coronary syndrome protocol to target atherosclerosis.

Prognosis and outcome

Takotsubo cardiomyopathy is an acute, reversible process and in the majority of cases the prognosis is excellent. Left ventricular systolic function on serial echocardiography improves over days to weeks, with one study showing resolution of mean ejection fraction from 20% to 60% by follow up at mean of 21 days (Wittstein et al, 2005). A proportion of patients will have ongoing episodic chest pain (possibly up to 30%), and some will have a formal recurrence of takotsubo cardiomyopathy with varying frequency reported from 3.5 to 10% (Gianni et al, 2006; Elesber et al, 2007).

However, for a significant minority of patients the outcomes are less favourable. There is an in-hospital mortality of 0.5–1% and 30-day mortality of 5% associated with sudden cardiac death or cardiogenic shock and multi-organ failure (Schultz et al, 2012). Moreover the potential of takotsubo cardiomyopathy to explain a cohort of stress-induced sudden cardiac death before hospitalization remains to be determined.

Takotsubo cardiomyopathy aetiology: recent research advances

Catecholamine surge is the aetiological cornerstone in takotsubo cardiomyopathy, with serum levels at presentation significantly elevated compared both to resting levels in the same patient and to levels in comparable patients with acute ischaemic heart failure (Wittstein et al, 2005). Moreover, iatrogenic takotsubo cardiomyopathy has been described after administration of sympathomimetics, for example in stress echocardiography (Abraham et al, 2009). The half-life of catecholamines is short such that serum levels will have halved several times over before initial assessment, in turn causing underestimation of the peak catecholamine levels to which the myocardium and vasculature are exposed.

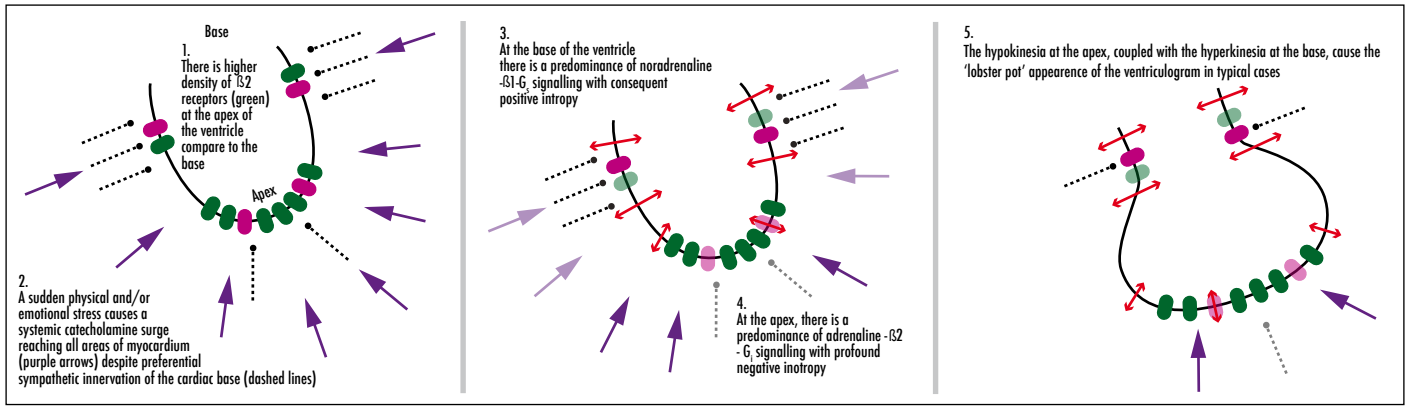
Linking this catecholamine surge to the observed myocardial dysfunction has remained an enigma for several decades. The resemblance to ST elevation myocardial infarction directs the clinician towards the coronary arteries, but the pattern of myocardial dysfunction requires multiple coronary vessels to be implicated simultaneously. One proposal to receive significant attention is the concept of 'aborted myocardial infarction', with plaque rupture and formation of a thrombus which subsequently dissipates leaving an acute myocardial stunning that subsequently resolves. Indeed abnormal left anterior descending artery anatomy could be present, such that the acutely occluded vessel supplies an unusually large area of the left ventricular anterior wall and apex (so-called 'wrap-around' left anterior descending) accounting for the large distribution, and a previous case report with intravascular ultrasound had identified acute plaque rupture in this context (Ibanez et al, 2005).

However, a study using intravascular ultrasound has not corroborated these results (Haghi et al, 2010), and a retrospective analysis of coronary anatomy in a cohort of patients with takotsubo cardiomyopathy showed no increased frequency of wrap-around left anterior descending anatomy (Hoyt et al, 2010). These studies are supported by a further prospective study (Delgado et al, 2011), largely dismissing aborted ST elevation myocardial infarction as a mechanism. Other proposals include direct effects of catecholamines to cause multivessel coronary artery spasm, myocardial microcirculatory dysfunction or myocyte dysfunction, but none of these can account for the regional abnormalities or address the conundrum of catecholamines exerting a profound negative inotropic effect in this condition.

The authors' hypothesis centres on the negative inotropic effect of high dose adrenaline on the left ventricular myocardium, and does account for these factors (Lyon et al, 2008; *Figure 4*). Studies in transgenic mice overexpressing the β2 adrenoceptor in ventricular cardiomyocytes have previously demonstrated differential response to low and high adrenaline concentrations. Physiological β2 stimulation causes G_s-mediated positive inotropy, but intense 'supraphysiological' stimulation alters the downstream effect to a G_i-mediated negative inotropy by a reversible process known as stimulus trafficking. This is specific to adrenaline, as noradrenaline does not activate this pathway.

A greater density of β2 adrenoceptors at the apex compared to the base accounts for the regional variation in

Figure 4. Schematic diagram showing the pathophysiology of takotsubo cardiomyopathy.



response, as adrenaline is released systemically from the adrenal glands into the circulation. Using a rodent model this hypothesis was confirmed, demonstrating acute apical and midventricular dysfunction in a 'takotsubo-like' pattern initiated by rapid high-dose intravenous adrenaline bolus, but not by noradrenaline (Paur et al, 2012). This acute adrenaline-dependent apical dysfunction was inhibited by prior treatment with a G_i inhibitor, confirming a G_i-dependent mechanism.

Replicating features on isolated cardiomyocytes in vitro, it has been demonstrated that acute adrenaline-mediated negative inotropy was β2-G_i dependent, resulting from stimulus trafficking of the β2 adrenoceptor from the normal 'stimulatory' G_s to the 'inhibitory' G_i pathway. Apical cardiomyocytes are more sensitive to catecholamines than basal cardiomyocytes isolated from the same ventricle, because it has a higher density of β-adrenoceptors (Paur et al, 2012). Thus this hypothesis suggests that, at the catecholamine levels seen in takotsubo cardiomyopathy, there is a β2-mediated negative inotropic effect, more pronounced at the apex, and completely reversible on removal of the catecholamine stimulus.

β2-G_i signalling, while negatively inotropic, is cardioprotective and activates anti-apoptotic pathways. The authors believe this may form a physiological negative feedback loop to dampen the cardiotoxic effects of acute stress and high catecholamines, and may contribute to explain the fully recovery and good long-term prognosis observed in most individuals with takotsubo cardiomyopathy. In addition, oestrogens have direct effects on expression of adrenoceptor proteins in the ventricular myocardium that may account for the female preponderance. For further discussion, refer to Lyon et al (2008) and Paur et al (2012).

Conclusions

Takotsubo cardiomyopathy is a unique and intriguing syndrome that still frequently eludes diagnosis. Our understanding of takotsubo cardiomyopathy has increased exponentially over the past decade, with much greater clarity in approach to its diagnosis and best management. Ultimately, however, there remains only a partial awareness of the true incidence of takotsubo cardiomyopathy in the emergency department, on the general medical take or in the catheter laboratory, and sparse clinical evidence for how to manage these patients. Coordinated epidemiological and pathophysiological studies will improve recognition, shed light on its mechanisms, and validate the theoretical and animal models that form the basis of practice today. The authors' research group would be interested to review any confirmed or suspected cases of takotsubo cardiomyopathy, and be delighted to offer management advice regarding patients with this challenging condition. **BJHM**

KEY POINTS

- Takotsubo cardiomyopathy is an acute, reversible process most often seen in postmenopausal women and triggered by a sudden catecholamine surge from an emotional or physical stress.
- The presentation is suggestive of acute ST elevation myocardial infarction, but at cardiac catheterization the coronary arteries are normal, and ventriculography shows a left ventricle resembling a Japanese octopus trap, or takotsubo.
- There is a spectrum of disease from mild chest pain to refractory cardiogenic shock.
- Management is aimed at supporting the haemodynamics until the abnormalities have resolved, using mechanical circulatory support if necessary.
- Prognosis is excellent and the majority of patients make a complete recovery.

Dr AR Lyon is a British Heart Foundation Intermediate Clinical Research Fellow. Dr AR Lyon and Dr AC Morley-Smith are supported by the National Institute for Health Research Cardiovascular Biomedical Research Unit at the Royal Brompton Hospital.

Conflict of interest: none.

Abraham J, Mudd JO, Kapur NK, Klein K, Champion HC, Wittstein IS (2009) Stress cardiomyopathy after intravenous administration of catecholamines and beta-receptor agonists. *J Am Coll Cardiol* **53**(15): 1320–5

Cesaretti M, Ansaldo G, Varaldo E et al (2010) Tako-tsubo cardiomyopathy as initial presentation of pheocromocytoma. A clinical case. *Ann Ital Chir* **81**(6): 439–43

Cevik C, Otahbachi M, Miller E, Bagdure S, Nugent KM (2009) Acute stress cardiomyopathy and deaths associated with electronic weapons. *Int J Cardiol* **132**(3): 312–17

Chadha S, Lodha A, Shetty V, Sadiq A, Hollander G, Shani J (2012) Complete heart block in takotsubo cardiomyopathy. *Heart Lung* Mar 14 (Epub ahead of print)

Citro R, Previtali M, Bovelli D et al (2009) Chronobiological patterns of onset of Tako-Tsubo cardiomyopathy: a multicenter Italian study. *J Am Coll Cardiol* **54**(2): 180–1

Delgado GA, Truesdell AG, Kirchner RM et al (2011) An angiographic and intravascular ultrasound study of the left anterior descending coronary artery in takotsubo cardiomyopathy. *Am J Cardiol* **108**(6): 888–91

Deshmukh A, Kumar G, Pant S, Rihal C, Murugiah K, Mehta JL (2012) Prevalence of Takotsubo cardiomyopathy in the United States. *Am Heart J* **164**(1): 66–71

Eitel I, von Knobelsdorff-Brenkenhoff F, Bernhardt P et al (2011) Clinical characteristics and cardiovascular magnetic resonance findings in stress (takotsubo) cardiomyopathy. *JAMA* **306**(3): 277–86

Elesber AA, Prasad A, Lennon RJ, Wright RS, Lerman A, Rihal CS (2007) Four-year recurrence rate and prognosis of the apical ballooning syndrome. *J Am Coll Cardiol* **50**(5): 448–52

Fefer P, Chelvanathan A, Dick AJ, Teitelbaum EJ, Strauss BH, Cohen EA (2009) Takotsubo cardiomyopathy and left ventricular outflow tract obstruction. *J Interv Cardiol* **22**(5): 444–52

Fröhlich GM, Schoch B, Schmid F et al (2012) Takotsubo cardiomyopathy has a unique cardiac biomarker profile: NT-proBNP/myoglobin and NT-proBNP/troponin T ratios for the differential diagnosis of acute coronary syndromes and stress induced cardiomyopathy. *Int J Cardiol* **154**(3): 328–32

Gianni M, Dentali F, Grandi AM, Sumner G, Hiralal R, Lonn E (2006) Apical ballooning syndrome or takotsubo cardiomyopathy: a systematic review. *Eur Heart J* **27**(13): 1523–9

Haghi D, Roehm S, Hamm K et al (2010) Takotsubo cardiomyopathy is not due to plaque rupture: an intravascular ultrasound study. *Clin Cardiol* **33**(5): 307–10

Hoyt J, Lerman A, Lennon RJ, Rihal CS, Prasad A (2010) Left anterior descending artery length and coronary atherosclerosis in apical ballooning syndrome (Takotsubo/stress induced cardiomyopathy). *Int J Cardiol* **145**(1): 112–15

Ibanez B, Navarro F, Cordoba M, M-Alberca P, Farre J (2005) Tako-tsubo transient left ventricular apical ballooning: is intravascular ultrasound the key to resolve the enigma? *Heart* **91**(1): 102–4
Kosuge M, Ebina T, Hibi K et al (2010) Simple and accurate electrocardiographic criteria to differentiate takotsubo cardiomyopathy from anterior acute myocardial infarction. *J Am Coll Cardiol* **55**(22): 2514–16
Kumar S, Kaushik S, Nautiyal A et al (2011) Cardiac rupture in takotsubo cardiomyopathy: a systematic review. *Clin Cardiol* **34**(11): 672–6
Kurisu S, Inoue I, Kawagoe T et al (2004) Time course of electrocardiographic changes in patients with tako-tsubo syndrome: comparison with acute myocardial infarction with minimal enzymatic release. *Circ J* **68**(1): 77–81
Kurisu S, Inoue I, Kawagoe T et al (2009) Prevalence of incidental coronary artery disease in tako-tsubo cardiomyopathy. *Coron Artery Dis* **20**(3): 214–18
Kurowski V, Kaiser A, von Hof K et al (2007) Apical and midventricular transient left ventricular dysfunction syndrome (tako-tsubo cardiomyopathy): frequency, mechanisms, and prognosis. *Chest* **132**(3): 809–16
Lyon AR, Rees PS, Prasad S, Poole-Wilson PA, Harding SE (2008) Stress (Takotsubo) cardiomyopathy – a novel pathophysiological hypothesis to explain catecholamine-induced acute myocardial stunning. *Nat Clin Pract Cardiovasc Med* **5**(1): 22–9
Madhavan M, Borlaug BA, Lerman A, Rihal CS, Prasad A (2009) Stress hormone and circulating biomarker profile of apical ballooning syndrome (Takotsubo cardiomyopathy): insights into the clinical significance of B-type natriuetic peptide and troponin levels. *Heart* **95**(17): 1436–41
Maron BJ, Towbin JA, Thiene G et al (2006) American Heart Association Scientific Statement: Contemporary Definitions and Classification of the Cardiomyopathies. *Circulation* **113**(14): 1807–16
Monney PA, Sekhri N, Burchell T et al (2011) Acute myocarditis presenting as acute coronary syndrome: role of early cardiac magnetic resonance in its diagnosis. *Heart* **97**(16): 1312–18
Naruse Y, Sato A, Kasahara K et al (2012) The clinical impact of late gadolinium enhancement in Takotsubo cardiomyopathy: serial analysis of cardiovascular magnetic resonance images. *J Cardiovasc Magn Reson* **13**: 67
Nguyen TH, Neil CJ, Sverdlov AL et al (2011) N-terminal pro-brain natriuretic protein levels in takotsubo cardiomyopathy. *Am J Cardiol* **108**(9): 1316–21
Omerovic E (2011) How to think about stress-induced cardiomyopathy? – Think "out of the box"! *Scand Cardiovasc J* **45**(2): 67–71
Otahbachi M, Cevik C, Bagdure S, Nugent K (2010) Excited delirium, restraints, and unexpected death: a review of pathogenesis. *Am J Forensic Med Pathol* **31**(2): 107–12
Paur H, Wright PT, Sikkel MB et al (2012) High levels of circulating epinephrine trigger apical cardiodepression in a β2-adrenergic receptor/Gi-dependent manner: a new model of takotsubo cardiomyopathy. *Circulation* **126**(6): 697–706
Prasad A, Lerman A, Rihal CS (2008) Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction. *Am Heart J* **155**(3): 408–17
Redfors B, Shao Y, Omerovic E (2012) Stress-induced cardiomyopathy in a patient with chronic spinal cord transaction at the level of C5: Endocrinologically mediated catecholamine toxicity. *Int J Cardiol* **159**(3): 61–2
Sato H, Tateishi H, Uchida T, Dote K, Ishihara M (1990) Takotsubo-type cardiomyopathy due to multivessel spasm. In: Kodama K, Haze K, Hon M, eds. *Clinical Aspect of Myocardial Injury: From Ischemia to Heart Failure.* Kagakuhyouronsha, Tokyo: 56-64
Schultz T, Shao Y, Redfors B et al (2012) Stress-induced cardiomyopathy in Sweden: evidence for different ethnic predisposition and altered cardio-circulatory status. *Cardiology* **122**(3): 180–6
Sharkey SW, Lesser JR, Garberich RF, Pink VR, Maron MS, Maron BJ (2012) Comparison of circadian rhythm patterns in tako-tsubo cardiomyopathy versus ST-segment elevation myocardial infarction. *Am J Cardiol* **110**(6): 795–9
Thiele H, Zeymer U, Neumann FJ et al (2012) Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med* **367**(14): 1287–96
Villareal RP, Achari A, Wilansky S, Wilson JM (2001) Anteroapical stunning and left ventricular outflow tract obstruction. *Mayo Clin Proc* **76**(1):79–83
Wittstein IS, Thiemann DR, Lima JA et al (2005) Neurohumoral features of myocardial stunning due to sudden emotional stress. *N Engl J Med* **352**(6): 539–48

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