Takotsubo Cardiomyopathy

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Editorial

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TAKOTSUBO CARDIOMYOPATHY:
WHAT IS ALL THE STRESS ABOUT?

For many centuries it has been recognized that emotional or physical stress can elicit cardiac symptoms including chest pain, dyspnea, palpitations, and syncope. In the last 60 to 75 years, the focus of clinical cardiology has been predominantly upon coronary artery disease as the most common cause of stress-induced cardiac chest pain and breathlessness, indeed with the development of an array of cardiac “stress” tests with the aim of identifying or excluding coronary artery disease. In parallel, over the last 30 years, the direct biological effects of catecholamines on the ventricular myocardium have been studied intensely, with detailed understanding of receptor, secondary messenger, and intracellular molecular biology underlying the inotropic and arrhythmogenic responses to catecholamines. This knowledge has demonstrated that high levels of epinephrine and norepinephrine can trigger distinct functional changes in myocardial function specific to adrenergic receptor subtypes and secondary messenger pathways activated.

This detailed knowledge of myocardial biology and catecholamine responses from laboratory studies has become clinically relevant since the first description of Takotsubo cardiomyopathy by Sato and colleagues from Hiroshima in 1990. Following their first report, there has been a growing avalanche of published case reports, small series, larger cohorts, and now national and international registries on this acute heart failure syndrome with characteristic phenotypic appearances. Having once been considered a rare condition with an unusual name, it is now rare to speak to a cardiologist working in acute cardiac care who has not seen a Takotsubo case in the previous year. While not as common as coronary disease, stress-induced heart failure in the absence of acute plaque rupture is becoming increasingly recognized. Published cohorts from many different countries and geographical regions have consistently suggested that approximately 1% to 2% of all individuals presenting with symptoms consistent of an acute coronary syndrome ultimately have Takotsubo cardiomyopathy or a related stress-induced cardiomyopathy syndrome. This has been supported with the report at the recent American College of Cardiology meeting in March 2014 of more than 21 000 cases of Takotsubo cardiomyopathy admitted to Medicare hospitals in the USA in 2011. 

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when identified from ICD-10 discharge coding. While this report requires appropriate peer review and analysis, it is highly suggestive that Takotsubo cardiomyopathy is significantly more common than previously thought. This study also highlighted the impact of severe unexpected environmental disasters to trigger mini-epidemics of Takotsubo cardiomyopathy in the affected communities, as seen in Vermont during Hurricane Irene and in Missouri following one of the worst tornadoes to hit America in living memory.

Further understanding of this condition has also identified that not all cases have the typical Takotsubo appearance with apical dysfunction and basal hypercontraction, which first led Sato and colleagues to compare the end-systolic appearance during ventriculography to the local Japanese fisherman’s octopus pot (Figure 1). The pot is designed in this way with a narrow neck to allow live octopi to swim into the pot when exploring for prey, but are then trapped and unable to escape. Live octopi are worth more than dead octopi in the Japanese fishing markets, and indeed, to some, eating octopi while alive is considered a delicacy. To others this might trigger an episode of Takotsubo syndrome! Figure 2 shows an artistic interpretation of an octopus inching its way into a vase, by contemporary potters Jan Wax and Chris Bing.

In this issue of Dialogues, a number of experts in the field review the literature and share their views and experience, and help identify the strategies required to diagnose and care for individuals with Takotsubo cardiomyopathy. Alexander R. Lyon gives the state-of-the-art review of the field and insights into the historical background to the emergence of this condition into modern cardiology practice. Eduardo Bossone, Rodolfo Citro, Francesco Ferrara, and Jorge A. Salerno-Uriarte describe the epidemiology of
Takotsubo cardiomyopathy, which persons are most at risk, and when are they likely to be most susceptible. Initially viewed as a relatively benign condition, due to the lack of severe obstructive coronary disease and recovery of macroscopic ventricular function, and certainly when compared with acute myocardial infarction, there is a growing literature suggesting that Takotsubo cardiomyopathy is not as mild as previously thought. Birke Schneider reviews the complications during the acute and chronic phases to shed light on the question of how serious this condition really is, and what to look out for in your patient with Takotsubo cardiomyopathy. Generally, these patients will enter acute primary percutaneous coronary intervention (PCI) protocols designed for patients with acute coronary syndromes. However, the management pathways for patients with Takotsubo cardiomyopathy are not clear, and Elmir Omerovic reviews the current knowledge that helps guide practice. We contacted Paul Bridgman and Christina W. Chan, who have published the experience from their hospital in Christchurch, New Zealand, following the two major earthquakes in 2011 and 2012. They provide a very personal account of their experience working in a hospital caught up in a major natural disaster, and the flow of acute Takotsubo cardiomyopathy cases through the acute coronary care unit. Gemma A. Figtree selects her Ten Seminal Papers on this syndrome and provides a personal review of the insights and advances that each paper provides covering the initial description and the major advances to date, including epidemiology, and mechanistic and clinical pathophysiology.

There is much still to be understood about this acute cardiac syndrome, which appears much more common than previously thought, and although recently recognized, has probably been around in human society for thousands of years.
Takotsubo cardiomyopathy has been described as an acute, reversible heart failure syndrome that is increasingly recognized with the access to urgent coronary angiography for patients with acute cardiac chest pain. Takotsubo cardiomyopathy patients have frequently experienced an extremely stressful triggering event and are typically postmenopausal women. These patients usually present with features typical of acute myocardial infarction including chest pain, dyspnea, palpitations, increased serum troponin, and acute electrocardiogram (ECG) changes including ST elevation and/or T wave inversion. The characteristic appearance is hypokinesia of the apical and mid-left ventricular myocardium with basal hypercontractility that resembles the Japanese fisherman’s octopus pot, the ‘takotsubo.’ This syndrome appears to reflect the cardiovascular response to a sudden surge in epinephrine levels, and may be a form of acute catecholaminergic stunning. Diagnosis requires exclusion of culprit obstructive coronary artery disease and recovery of the regional dysfunction. Patients may present to emergency services de novo, but Takotsubo cardiomyopathy may result in several acute medical and surgical conditions, and can be triggered by various drugs. Initially, there is a high-risk phase with several potential serious complications; therefore, access to high quality cardiac imaging is important to confirm the diagnosis, screen for complications, and confirm recovery at follow-up. Takotsubo cardiomyopathy cases with evidence of heart failure may require a short course of medical therapy; in severe cases, mechanical support as a “bridge to recovery” may be necessary.

It is rare in modern cardiology for a relatively common condition to be ‘discovered’ as a completely new clinical entity. However, this is the remarkable story concerning the syndrome we now recognize in our clinical practice as Takotsubo cardiomyopathy. First described by Hiraku Sato and colleagues in 1990,1 Takotsubo cardiomyopathy has been unearthed by the modern implementation of early access to coronary angiography for patients with chest pain and acute ischemic electrocardiogram (ECG) changes, and the significant advances in modern cardiac imaging. It is now clearly apparent that Takotsubo cardiomyopathy is not a new condition, but has most likely been occurring for the entire length of ‘man’s existence’ on our planet, or perhaps more appropriately ‘women’s existence,’ given the strong predisposition towards the female sex. This sex bias and many other features of this intriguing condition remain to be explained, which adds to the curiosity of the syndrome. Indeed, there has been an explosion of literature on the topic, with 1992 articles on Pubmed at the time of writing, with the majority published within the last decade.2 This also reflects the relative infancy of the clinical experience and knowledge for this condition, which is combined with a spectrum of interesting features and a growing appreciation that it is not as rare as previously thought. Like many of life’s fascinating intrigues, the more this condition is looked for, the more it is found, whether in the emergency department, the cardiac catheterization laboratory, or across the hospital in the general medical wards, surgical wards, or intensive care units.

**HISTORICAL PERSPECTIVE**

Takotsubo cardiomyopathy was first described by a group of cardiologists working in the Hiroshima City Hospital of the coastal Chugoku region in eastern Japan.1 They were early advocates of primary percutaneous intervention for acute coronary syndromes (ACSs), and since 1981, many patients with chest pain and ECG changes entering their hospital were transferred to the cardiac catheterization laboratory to assess coronary anatomy. In 1983, Sato et al admitted an unusual patient who presented with a strange systolic
abnormality that reminded them of a ‘takotsubo,’ which is the local Japanese fisherman’s octopus pot (Figure 1). The takotsubo has a narrow neck with a wide bottom half, and when it is placed on the sea floor, live octopi will swim in and become trapped. During an acute episode of the typical Takotsubo cardiomyopathy variant, the left ventriculogram at end systole resembles this takotsubo shape due to the hyperdynamic contraction of the ventricular base and hypokinesia of the midventricular and apical myocardium (Figure 1B).

Until 2003, Sato et al had performed about 1800 cases of diagnosis/treatment of ACSs. Thirty cases (1.7%) were diagnosed as Takotsubo cardiomyopathy. In the late 1990s, ‘Takotsubo cardiomyopathy’ became more frequently reported in the Japanese medical society and medical journals. In 2001, 88 cases of Takotsubo cardiomyopathy were reported in a Japanese multi-center study. Apparently, the name ‘takotsubo’ was not accepted by the review committee. As a result, the morphological features were considered to be the bulging left ventricular (LV) apex and were reported as “transient left ventricular ballooning.” It was not until a report by Desmet et al in 2003 that this disease was recognized to develop in persons other than the Japanese, and since that report there has been an avalanche of global reports and series demonstrating that this is not a condition unique to the Japanese. In speculating why the Japanese were the first to recognize this condition, another factor may have played a role. Japan lies on a fault line between the Pacific and Honshu tectonic plates, and as such is periodically susceptible to earthquakes. A major earthquake is one of the most sudden, unexpected, and severe stresses that human populations are exposed to, and would be expected to activate a sympathetic storm that would increase circulating adrenaline levels much higher than normal levels in day-to-day life. After the Niigata Chuetsu earthquake in 2004, there were over 50 cases of Takotsubo cardiomyopathy diagnosed in the following 3 weeks, with almost half in the first week. Most recently, after the Great East Japan Earthquake and tsunami of 2011, there was an increase in acute heart failure admissions. A similar ‘mini’ epidemic of Takotsubo cardiomyopathy cases followed the earthquakes in Christchurch, New Zealand, which are discussed in the Fascinoma article in this issue of Dialogues in Cardiovascular Medicine.

Takotsubo cardiomyopathy is the label that most practicing doctors currently use to describe this condition. However, several other labels have been used. As noted above, ‘apical ballooning syndrome’ was used by a number of Japanese investigators for a period, until the name takotsubo became accepted. An analysis of ventriculograms, echocardiograms, and cardiac magnetic resonance (CMR) images from >90 patients with acute Takotsubo cardiomyopathy showed that the apical and midventricular epicardial end-systolic dimensions rarely increased. However, the regionally-matched–endocardial dimensions are significantly greater, giving an appearance of a ‘relative’ ballooning, which does not present an absolute assessment. Therefore, I would recommend avoiding using this term as it has the potential to be misleading. Other names include ampulla-shaped cardiomyopathy, ‘broken heart syndrome’ during bereavement, and in the US cardiomyopathy guidelines, it was named ‘stress cardiomyopathy’ under the list of secondary cardiomyopathies. However, in recent years, the name Takotsubo cardiomyopathy has dominated. It is likely to be maintained

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<th>SELECTED ABBREVIATIONS AND ACRONYMS</th>
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<td><strong>ACE inhibitors</strong></td>
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<td><strong>ACS</strong></td>
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<td><strong>IABP-SHOCK II trial</strong></td>
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<td><strong>NSTEM</strong></td>
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<td><strong>NT-proBNP</strong></td>
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<td><strong>T2STIR</strong></td>
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<td><strong>VA-ECMO</strong></td>
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for the near future because it has become embedded in medical literature, teaching, and the unusual name provides a story that helps to act as a memory aide. In addition, most current cardiology trainees have heard of the ‘Japanese octopus pot.’

**DEFINITION, DIAGNOSTIC CRITERIA, AND TRIGGERS**

Takotsubo cardiomyopathy and associated variants are a form of an acute reversible heart failure syndrome, which may represent a form of acute catecholaminergic myocardial stunning in the absence of culprit occlusive coronary artery disease to explain the pattern of the temporary LV dysfunction observed. Patients with Takotsubo cardiomyopathy have a number of typical features that are important to identify in order to confirm the diagnosis. Two diagnostic criteria have been proposed by the Mayo and Gothenburg groups, and are summarized in Table I.9,10

They have several common features:
1. Transient and, therefore, reversible, contractile dysfunction involving a widespread region of the left ventricular myocardium and in some cases the right ventricle.

<table>
<thead>
<tr>
<th>MODIFIED MAYO CLINIC CRITERIA9: all four required for diagnosis</th>
<th>GOTHENBURG CRITERIA10: all three required for diagnosis</th>
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<tr>
<td>A</td>
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<td>Transient hypokinesia, akinesis, or dyskinesia in the left ventricular midsegments 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</td>
<td>Transient hypokinesia, akinesis, or dyskinesia in the left ventricular segments and frequently, but not always, a stressful trigger (psychological or physical)</td>
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<td>The absence of obstructive coronary disease or angiographic evidence of acute plaque rupture</td>
<td>The absence of other pathological conditions (eg, ischemia, myocarditis, toxic damage, tachycardia, etc) that may more credibly explain the regional dysfunction</td>
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<td>New ECG abnormalities (ST-segment elevation and/or T wave inversion) or modest elevation in cardiac troponin</td>
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<td>The absence of pheochromocytoma and myocarditis</td>
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Table I. Published diagnostic criteria for Takotsubo cardiomyopathy. Based on data from references 9 and 10.
2. Myocardial dysfunction where the degree and distribution cannot be explained by ‘culprit’ obstructive coronary artery disease or other cardiac conditions, e.g., hypertrophic cardiomyopathy, toxins, myocarditis, or tachycardia. As emphasized in the Mayo criteria, extension of the region affected beyond a single epicardial coronary artery territory is typical and aids diagnostic confirmation, although rare cases may appear to be regionally restricted to a single segment. Distinguishing Takotsubo cardiomyopathy from ‘myocarditis’ is a clinical challenge, and I believe this should be refined to ‘infective myocarditis’ because there is evidence of acute myocardial edema and inflammation in the affected region in Takotsubo cardiomyopathy patients, i.e., increased water content as shown by CMR T2-weighted short tau inversion recovery sequences (T2STIR). These results have been confirmed in animal models and suggest that acute Takotsubo cardiomyopathy shares features with catecholaminergic myocarditis. A careful history and other clinical features can normally differentiate between acute viral myocarditis and acute Takotsubo cardiomyopathy (i.e., a stressful trigger if present) vs the viral prodromal illness.

3. New and reversible acute ECG changes, as described below, and usually a small troponin increase are also required for diagnosis, and it is rare to have typical cases without ECG changes or a troponin rise. Due to the dependence upon the timing of presentation relative to the onset of the symptoms, ST elevation is not mandatory. However, it is helpful when present as it usually activates a primary percutaneous coronary intervention pathway leading to early exclusion of obstructive coronary artery disease as the cause of the acute presentation and ECG changes. However, in clinical practice milder cases exist that can easily be missed, particularly if ECG and ventricular contractility abnormalities are subtle, short lasting, and resolve before cardiac imaging is performed.

4. The final diagnostic criterion from the Mayo criteria is the absence of pheochromocytoma or myocarditis. While appropriate to exclude the latter, it is clear that patients with pheochromocytoma, and particularly those with an epinephrine-secreting pheochromocytoma, may develop acute Takotsubo cardiomyopathy resulting from a catecholamine storm in an analogous manner to an individual who has a catecholamine storm following a sudden stressful experience. The pathophysiology and clinical phenotypes are identical, and so it would appear illogical to exclude these patients from the diagnosis. Instead, it is my belief that patients with Takotsubo cardiomyopathy can be categorized into two groups: (i) primary Takotsubo cardiomyopathy cases, and (ii) secondary Takotsubo cardiomyopathy cases. Primary Takotsubo cardiomyopathy patients would include those presenting with a primary diagnosis of Takotsubo cardiomyopathy, usually de novo to the emergency department, and without a coexisting medical condition, which has triggered the syndrome. In contrast, a wide variety of acute medical and surgical conditions can trigger catecholamine storms, and result in a Takotsubo cardiomyopathy syndrome as a secondary consequence of a preexisting medical condition. Therefore, these could be considered secondary Takotsubo cardiomyopathy cases, and this helps guide the clinician to treat not only the acute heart failure syndrome, but also the underlying medical condition. A large number of case reports have been published describing acute Takotsubo cardiomyopathy in the context of a secondary illness, and Table II presents a number of the published triggers. In addition, an increasing number of cases are triggered by drug administration (Table III).

<table>
<thead>
<tr>
<th>Table II. Triggers for acute Takotsubo cardiomyopathies.</th>
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<tr>
<td>• Acute asthma and chronic obstructive airways disease</td>
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<td>• Thyrotoxicosis</td>
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<td>• Addisonian crisis</td>
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<td>• General anesthesia induction</td>
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<td>• Septic shock</td>
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<td>• Myasthenic crisis</td>
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<td>• Acute Guillain-Barre Syndrome</td>
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<td>• Acute systemic lupus erythematosus crisis</td>
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<td>• Anaphylaxis</td>
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<td>• Dobutamine stress echocardiography</td>
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<td>• Direct Current Cardioversion</td>
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<td>• Exercise electrocardiogram treadmill test</td>
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<td>• Electroconvulsive therapy</td>
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<tr>
<td>• Acute cholecystitis</td>
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<td>• Acute pancreatitis</td>
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<tr>
<td>• Pregnancy</td>
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<td>• Near drowning</td>
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<td>• Attempted suicide (hanging)</td>
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<tr>
<td>• Taser stunning</td>
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<tr>
<td>• Restraint in custody</td>
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<tr>
<td>• Subarachnoid hemorrhage</td>
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<tr>
<td>• Head injury</td>
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<tr>
<td>• Stroke</td>
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Some are intuitive (e.g., catecholamines and sympa-
omimetics), but the mechanistic explanation for others is more challenging. From this list, it is evident that acute Takotsubo cardiomyopathy can present in all departments of the hospital, ranging from the acute respiratory, endocrinology, neurology, and surgical wards, operating rooms, general and neuro-intensive care units, obstetric wards, and psychiatric departments.

A stressful trigger, physical or psychological, is helpful when it is present with a clear temporal relationship to the acute presentation. However, various series have identified that up to one-third of cases have no overt stressful trigger and appear to be ‘spontaneous.’ Therefore, a stressful trigger is not mandatory for the diagnosis, and is recognized in both sets of diagnostic criteria.

Like all diagnoses in clinical practice, some cases will obviously be Takotsubo cardiomyopathy with a clear stress precipitant, normal coronary arteries, marked apical hypokinesia on ventriculography and echocardiography, and no late gadolinium enhancement on CMR. Conversely, many cases are less clear and fall into a clinical ‘grey zone,’ perhaps complete with a convincing history, but patients may present with: (i) areas of coronary atherosclerosis; (ii) a less convincing pattern or degree of hypokinesia; and (iii) patchy late gadolinium enhancement on the acute phase CMR. These presentations lead to the questions: (i) is this a causative or bystander disease; (ii) has the dysfunction already resolved or is this an atypical pattern; and (iii) does this represent an area of inflammation in myocarditis or Takotsubo cardiomyopathy? Multidisciplinary discussions may be necessary in the acute phase to resolve the diagnostic dilemma and decide on the initial management. Reversibility is a key hallmark of Takotsubo cardiomyopathy, and it may require time and follow-up with repeated cardiac imaging to resolve these unclear cases.

### ANATOMICAL VARIANTS

The initial description of Takotsubo cardiomyopathy described what is now considered the classical pattern of LV regional wall motion abnormalities (RWMA), with apical and circumferential midventricular hypokinesia and basal hypercontractility. At end systole, the ventricle has the typical appearance of a takotsubo with a narrow neck and globular lower portion.

Increasing experience and reporting led to the growing recognition that this typical Takotsubo cardiomyopathy variant with apical dysfunction is present in ~80% of cases, but other anatomical variants may also occur. These are listed with some typical examples as shown in Figure 2 (page 80). The two most common ‘atypical’ variants are: (i) the inverted takotsubo or basal variant, with basal hypokinesia and apical hypercontractility,13,14 also referred to as the ‘nutmeg’ or ‘artichoke’ heart, and (ii) the midventricular variant with circumferential midventricular hypokinesia and both apical and basal hypercontractility.15,16 The second variant has a unique end-systolic appearance, which has been likened to either a Greek vase or the ‘ace of spades,’ although the inverted takotsubo variant can also have the ‘ace of spades’ appearance (Figure 2A).17 In both inverted takotsubo and midventricular variants, a similar principle exists where reversible LV dysfunction affects more than one coronary territory, in the absence of culprit coronary artery disease, and again stressful precipitants are helpful, but not mandatory.

Other variants have been described, including biventricular apical dysfunction, apical dysfunction sparing the apical tip (possibly a form of the midventricular takotsubo variant),18 and isolated right ventricular Takotsubo cardiomyopathy (Figure 2B and 2C).19,20,21 Perhaps the most provocative and intriguing question is whether, in the most severe cases, an acute catecholamine storm can trigger an acute, reversible global dysfunction, which appears to be similar to a dilated cardiomyopathy, but fully recovers and fulfills all the other diagnostic criteria required. In this scenario, the differential diagnosis is de novo dilated cardiomyopathy, history of coexisting risk factors for Takotsubo cardiomyopathy, and a clinical course that may aid in the differentiation. However, if the pathophysiology of acute

### Table III. Drugs associated with triggering Takotsubo cardiomyopathy.

<table>
<thead>
<tr>
<th>Catecholamines, sympathomimetics, and vagolytics</th>
<th>Non-catecholaminergic and sympathomimetic drugs</th>
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<tbody>
<tr>
<td>Epinephrine</td>
<td>Flourouracil (5-FU)</td>
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<tr>
<td>Dobutamine</td>
<td>Combretastatin</td>
</tr>
<tr>
<td>Metaraminol</td>
<td>Cefotiam</td>
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<td>Ephedrine</td>
<td>Pazopanib</td>
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<td>Ergonovine</td>
<td>Anagrelide</td>
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<td>Oxymetazoline</td>
<td>Levothyroxine</td>
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<td>Atropine</td>
<td>Lumiracoxib</td>
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<tr>
<td>Venlafaxine</td>
<td>Dipyriramole</td>
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<tr>
<td>Duloxetine</td>
<td>Potassium chloride</td>
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<tr>
<td>Nortriptyline</td>
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</table>

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catecholaminergic stunning is the same, then it would appear to be another variant of stress cardiomyopathy, and can be included as a global variant of Takotsubo cardiomyopathy.

**EPIDEMIOLOGY**

It is believed that the incidence of Takotsubo cardiomyopathy is almost certainly underestimated, but with an increasing awareness and widespread access to early coronary angiography, it is now more frequently rec-ognized. Several series in Asian and western (predominantly white) populations suggest around 1% to 2% of patients with suspected ACS are eventually diagnosed with Takotsubo cardiomyopathy. Within the United Kingdom, this would equate to approximately 3000 cases per year, and across Europe to approximately 30,000 cases per year. The distribution is strikingly heterogeneous such that postmenopausal women account for 70% to 90% of reported cases, although male and younger female cases have been observed. Unlike ACS and other atherosclerosis-related conditions, presentations are more common in the summer months, and lack the early morning peak associated with plaque rupture events.

**PATHOPHYSIOLOGY**

Given the frequent, sudden, and unexpected stressful precipitant, the signs of sympathetic activation at presentation, secondary medical triggers, which also lead to extreme sympathetic activation, and the role of catecholamines appear central to the pathophysiology of Takotsubo cardiomyopathy. There are two elements of the equation to consider: (i) the cognitive centers of the brain, the hypothalamic-pituitary-adrenal axis (HPAA), and the level of epinephrine and norepinephrine released for a given stress (ie, HPAA gain), and (ii) the heart and cardiovascular system’s response to the sudden sympathetic activation and surge in catecholamines.
Serum catecholamine levels at presentation are significantly elevated compared with resting levels in the same patient and with levels in comparable patients with acute heart failure secondary to acute myocardial infarction (AMI), suggesting a potential for excessive HPAA gain and epinephrine release. Several cases of iatrogenic Takotsubo cardiomyopathy have been reported after administration of sympathomimetics, ie, dobutamine used for stress echocardiography. The half-life of circulating catecholamines is very short, and the peak catecholamine levels that the myocardium and vasculature are exposed to will be significantly higher than levels measured at the time of presentation to emergency services, diagnosis, and initial assessment.

Several hypotheses have been proposed to explain the unique cardiac appearance in Takotsubo cardiomyopathy and the cardiac response to severe stress. These can be broadly divided into vascular and myocardial causes, and may not be mutually exclusive given that the entire cardiovascular system is exposed to the same ‘catecholamine storm.’

### Vascular hypotheses

The resemblance to ST-segment myocardial infarction (STEMI) directs the clinician towards the coronary arteries, but the pattern of myocardial dysfunction requires multiple coronary vessels to be implicated simultaneously. One proposal is the concept of ‘aborted myocardial infarction,’ with plaque rupture and thrombus formation, which subsequently dissipates leaving an unobstructed coronary artery with acute myocardial stunning that subsequently resolves. However, this would have a regional distribution based on the infarct-related artery. The typical pattern of apical dysfunction in Takotsubo cardiomyopathy does not fit with a single coronary territory because, by definition, Takotsubo cardiomyopathy is a “dysfunction extending beyond one coronary artery territory.”

If limited to a single vessel, this would also require a large territory of the myocardium to be supplied by the culprit artery, such as the “wrap-around” variant of the left anterior descending coronary artery (LAD), which supplies the anterior wall, apical myocardium, and up to 25% of the inferior wall. A previous case report using intravascular ultrasound (IVUS) had identified acute plaque rupture in this context, supporting this vascular hypothesis. However, a recent study using IVUS refuted this hypothesis, reporting absence of plaque rupture, positive remodeling, or intracoronary thrombus in ten patients presenting with acute Takotsubo cardiomyopathy. Furthermore, a retrospective analysis of coronary anatomy in a cohort of Takotsubo cardiomyopathy patients showed no increased frequency of wrap-around LAD anatomy. Recently, the circulating microRNA profile was reported and showed significant differences between patients with Takotsubo cardiomyopathy and those with AMI, suggesting a different pathophysiological entity. These studies are supported by a further prospective study, which dismisses aborted STEMI as a mechanism.

Another conceivable vascular mechanism is a multivessel coronary artery spasm, potentially with myocardial microcirculatory dysfunction and with Takotsubo cardiomyopathy resulting from a form of ischemic stunning with superimposed catecholamines. The finding of multivessel vasospasms in several cases during diagnostic coronary angiography, particularly in the earliest reports, supports this hypothesis. In one series, 3 out of 30 patients had spontaneous multivessel coronary vasospasm and 43% had a vasospasm as a result of pharmacological provocation with ergonovine or acetylcholine.

Another large case study revealed multivessel coronary spasm following acetylcholine provocation in 10% of patients. In some cases, vasospasm correlated with the region of dysfunction, but, equally in other cases, it did not, leading the authors to conclude that vasospasm plays no role in the etiology of Takotsubo cardiomyopathy.

At odds with the multivessel vasospasm hypothesis as the sole mechanism, a number of clinical cases reported were triggered by either dobutamine, a vasodilator with no vasospastic effects, or epinephrine, which also has a dominant coronary vasodilatory effect, and, therefore, would not support vasospasm as the primary mediator. In addition, after any stress and a high surge in catecholamines, generalized impairment of endothelial function is to be expected, and both coronary and peripheral arteries may be prone to vasospasm upon provocation. It is important to distinguish between cause and association before all cases of Takotsubo cardiomyopathy can be explained by multivessel vasospasm. There are significant differences in the histopathological features of endomyocardial biopsies taken from patients with Takotsubo cardiomyopathy showing a pattern of myocardial abnormalities not associated with infarcted, stunned, or hibernating myocardium, which would not support a primary vascular cause.
Myocardial hypotheses

**Acute left ventricular outflow tract obstruction**

Acute left ventricular outflow tract obstruction (LVOTO) has been proposed as the cause for Takotsubo cardiomyopathy. This came from the observation of an acute LVOTO pressure gradient in four Takotsubo cardiomyopathy cases, with a subsequent regeneration of the gradient during dobutamine stress echocardiography. This pathophysiological hypothesis states that patients who are prone to develop LVOTO may also develop a dynamic midcavity LV obstruction under catecholamine excess. Older women with smaller hearts, a demographic who frequently have prominent septal bulges, potentially could be predisposed to acute LVOTO. This would functionally separate the left ventricle into two chambers: a basal chamber under normal wall stress and an apical chamber under high stress, which would reduce subendocardial flow in the apex. This could explain the transient nature of the apical dysfunction as the wall stress in the apex would be subsequently reduced by the ensuing ischemia and apical dysfunction, limiting pressure necrosis, and infarction. However, in larger cohorts reported, LVOTO was only observed in 25% of cases in the acute phase of Takotsubo cardiomyopathy. This suggests that while it is contributory in a subset of patients, LVOTO is unlikely to be the underlying cause of Takotsubo cardiomyopathy, but may be a modifier contributing to a more severe phenotype.

**Direct catecholamine-mediated stunning**

Several years ago, our group proposed a mechanism for Takotsubo cardiomyopathy based upon the negative inotropic effect of high-dose epinephrine on the LV myocardium (Figure 3). Studies in transgenic mice overexpressing the β2-adrenoceptor in ventricular cardiomyocytes have demonstrated a differential response to low and high epinephrine concentrations. Physiological β2-adrenoceptor stimulation causes Gi-mediated positive inotropy, but intense 'supraphysiological' stimulation alters the downstream effect to a Gs-mediated negative inotropy by a reversible process known as stimulus trafficking. Stimulus trafficking is specific to epinephrine because norepinephrine does not activate this pathway (Figure 4).

We integrated this observation of epinephrine-mediated negative inotropy via the β2-adrenoceptor with the distribution of the receptor in the heart to explain the apical dysfunction. A number of reports from different mammalian species (e.g., cat, dog, rabbit, rat, and mouse) demonstrate that the mammalian heart has a higher density of β-adrenergic receptors or β-adrenergic receptor responsiveness in the apical myocardium compared with the basal myocardium. This β-adrenergic receptor gradient is opposite of the sympathetic innervation gradient, which is highest in the atria and basal ventricular myocardium, and decreases toward the apical myocardium. The sympathetic innervation gradient has been reported in normal human hearts with a density of sympathetic nerve endings approximately 40% higher in the basal myocardium than in the apical myocardium, as identified by tyrosine hydroxylase during autopsy. Sympathetic innervation of the myocardium in the canine left ventricle shows a similar pattern, with the highest density of nerve endings found at the base, decreasing to the lowest levels at the apex. In a normal physiological setting, the majority of norepinephrine is released from nerve terminals, with circulating norepinephrine released from the adrenal medulla making a minimal contribution. Hence, it appeared that the β-adrenergic receptors, and not the sympathetic nerve endings, dictated the apical sensitivity to surges in catecholamines.

We developed a rodent model of Takotsubo cardiomyopathy, demonstrating acute, reversible apical and midventricular dysfunction in a 'takotsubo-like' pattern initiated by a rapid intravenous injection of a high-dose catecholamine dose.
epinephrine bolus to replicate the acute surge in serum epinephrine in response to sudden stress. A similar observation of acute apical dysfunction had been reported in a Takotsubo cardiomyopathy model initiated by conscious restraint in rats and after epinephrine infusion in monkeys. Subsequently, high dose intraperitoneal isoproterenol has also been reported to cause acute apical dysfunction in a rodent model, which would support a β-adrenoreceptor-mediated mechanism. By contrast, in our model, the acute apical dysfunction could not be triggered by a high-dose norepinephrine bolus. We identified a greater density of β2-adrenoreceptors in cardiomyocytes isolated from the apex compared with the basal myocardium of the same heart using a radiolabelled ligand-binding assay directly measure receptor density. We suggest that this may account for the regional variation in response, and concurs with the fact that epinephrine is systemically released from the adrenal glands into the circulation while the myocardium is exposed to a similar epinephrine concentration in the perfusing blood, and therefore receptor expression levels and density confer differences in the regional responses.

This acute epinephrine-dependent apical dysfunction could be inhibited by prior treatment with pertussis toxin, a selective Gi inhibitor, confirming that this is a Gi-dependent mechanism. While replicating features on isolated cardiomyocytes in vitro, we demonstrated that acute epinephrine-mediated negative inotropy was β2-Gi dependent, resulting from stimulus trafficking of the β2-adrenoreceptor from the normal ‘stimulatory’ Gi to the ‘inhibitory’ Gi pathway. Apical cardiomyocytes are more sensitive to catecholamines than basal cardiomyocytes isolated from the same ventricle due to a higher density of β-adrenoreceptors. Our hypothesis suggests that, at the extremely high serum catecholamine levels observed in patients with Takotsubo cardiomyopathy, there is a negative β2-adrenoreceptor-mediated inotropic effect, which is more pronounced at the apex and completely reversible upon removal of the catecholamine stimulus. β2-Gi signaling, while negatively inotropic, is cardioprotective and activates antiapoptotic pathways. There is evidence that these pathways are activated in the hearts of Takotsubo cardiomyopathy patients from endomyocardial biopsies during the acute phase, but not at follow-up, which is consistent with a temporary cardioprotective effect during the stunning phase. We believe this may form a physiologically negative feedback loop to dampen the cardiotoxic effects of acute stress and high catecholamines, and may explain the full recovery and good long-term prognosis observed in most individuals with Takotsubo cardiomyopathy. In addition, we know that estrogen has a direct effect on adrenoreceptor protein expression in the ventricular myocardium that may account for the female preponderance. Several papers provide detailed discussions of the biological mechanisms involved in this process.

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**Figure 4. Inotropic effects of epinephrine and norepinephrine.**

A. Ventricular myocardium from transgenic mice over-expressing human β2-adrenoreceptor (TG4 mice), and the effects of PTX. B. Epinephrine and PTX treatment simulations and their effects on the ventricle.

**Abbreviation:** PTX, pertussis toxin.


GENETIC PREDISPOSITION

Although the stressful trigger implies a strong environmental component to the pathophysiology, it is conceivable that some individuals may be predisposed to the development of Takotsubo cardiomyopathy following a stressful trigger. There have been published examples of several family members presenting with Takotsubo cardiomyopathy (eg, mother and daughter, or the intriguing report of two sisters simultaneously developing Takotsubo cardiomyopathy after being told of the death of their father, although they were physically hundreds of kilometers apart).

Several groups have published small genomic analyses on plausible targets. One study showed a slight increase in specific polymorphisms for both the β1- and the β2-adrenoreceptors in their Takotsubo cardiomyopathy cohort. However, these findings have not been replicated in four other genetic studies where none of the common and pathologically relevant variants of the cardiac β1-, β2- or α1-adrenoreceptors were detected at a higher prevalence in Takotsubo cardiomyopathy patients. The Italian group reported a slightly higher prevalence of a gain-of-function polymorphism of the G protein-coupled receptor kinase 5 (GRK5 31L>Q) in their small cohort of Takotsubo cardiomyopathy patients (n=22) (GRK5 31L>Q was 64% vs 44% in normal controls). This could be relevant as increased GRK5 activity would enhance trafficking of the β2-adrenoreceptors to the G, pathway and link to the proposed hypothesis above. However, a recent genetic analysis of an Australian cohort of 92 Takotsubo cardiomyopathy patients failed to replicate this finding, and this study did not find any relevant polymorphisms in the estrogen receptor α (ERα) or the catechol-O-methyl transferase genes. However, all of these studies are limited by relatively small patient numbers compared with those usually required to confirm genetic causation in cardiovascular disease.

CLINICAL PRESENTING FEATURES AND COMPLICATIONS

Patients presenting to the emergency services have a typical pattern describing the sudden onset of acute, cardiac originating symptoms, including chest pain, dyspnea, and palpitations, which are usually triggered by a distinct stressful episode. Clinical examination and cardiac investigations depend upon the delay between the onset of symptoms/stressful trigger and presentation to medical services, which is analogous to the evolving pattern of clinical features in patients with AMI. Identifying the temporal sequence is helpful to interpret the clinical findings. Patients presenting within 12 hours frequently have signs of sympathetic activation, with sinus tachycardia, systemic arterial hypertension, diaphoresis, anxiety, and, in more severe cases, acute pulmonary edema, and/or atrial or ventricular arrhythmias. Patients presenting in the early time window typically have ST elevation in lateral and precordial leads, frequently spanning a broad distribution of ECG territories (Figure 5A).

The temporal evolution of the syndrome is becoming increasingly apparent as a greater number of clearly detailed cohorts are reported. After the initial catecholaminergic storm, patients appear to move into a low cardiac output state, with relative bradycardia and possible peripheral vasodilation. The ECG also changes between 24 and 72 hours with resolution of the ST elevation accompanied by widespread deep T wave inversion and progressive prolongation of the QT and QTc intervals (Figure 5B), frequently to dangerous levels (>500 ms). These changes predispose patients to malignant ventricular tachyarrhythmias including polymorphic ventricular tachycardia, torsades de pointes, and ventricular fibrillation. Life-threatening ventricular tachyarrhythmias have been reported in up to 5% of cases.

A variety of acute complications has been reported in patients with acute Takotsubo cardiomyopathy, and they are summarized in Table III. Even for a relatively new syndrome, certain dogmas have developed and possibly skewed the experience of the individual physician. One such dogma is that Takotsubo cardiomyopathy is a benign condition. By comparison with patients with acute STEMI due to coronary occlusion passing through the cardiac catheter laboratory, Takotsubo cardiomyopathy patients appear to be in a favorable situation. They lack acute coronary occlusions, and frequently, but not always, have minimal or absent obstructive coronary disease. Combined with full recovery of left ventricular function at follow-up, this would seem a favorable scenario compared with advanced coronary disease, AMI, and permanent ventricular injury. However, the caring physician must remember that Takotsubo cardiomyopathy is an acute heart failure syndrome, and while long-term prognosis is favorable compared with the AMI patient, it is not benign, and a number of pitfalls may affect the patient during the acute episode. They must survive the storm to enjoy the benefits of recovery. Future storms during recurrent episodes can be equally hazardous.
Once the diagnosis of Takotsubo cardiomyopathy has been confirmed, it is important to identify patients at high risk for complications. Factors associated with a worse outcome include older age, greater myocardial injury as identified by greater cardiac troponin release and lower ejection fraction, and those cases triggered by a physical stress rather than an emotional event. The Mayo Clinic proposed a risk score based on these findings (omitting troponin due to variation in laboratory assays between centers). With 1 point allocated for each risk factor present (age >70 years, presence of physical stressor, and ejection fraction <40%), acute heart failure occurred in 28%, 58%, and 85% of patients with 1, 2, and 3 points, respectively. This requires validation across a wider cohort of patients, but the recommended principle is to identify those patients at higher risk early to ensure close monitoring and early intervention if complications arise.

**MANAGEMENT**

Provisional diagnosis is confirmed by an integration of the clinical history, ECG appearance, coronary angiogram, ventriculogram, and biomarkers. There are certain features specific to Takotsubo cardiomyopathy compared with AMI that can provide the clinician with confidence to make the diagnosis during the acute phase, although follow-up imaging is required to prove reversibility and recovery before the final diagnosis is categorically confirmed.
Coronary angiography and ventriculography

Takotsubo cardiomyopathy patients will have a coronary angiography to exclude STEMI or non-ST segment elevation myocardial infarction (NSTEMI). In Takotsubo cardiomyopathy, the epicardial coronary arteries are typically normal, although given the predilection for older patients, bystander atherosclerotic coronary artery disease can be present. Where present, it is important to clarify that the coronary artery disease is insufficient to cause the degree or pattern of LV dysfunction and is incidental. Several studies reviewing cohorts of Takotsubo cardiomyopathy patients report bystander coronary artery disease in up to 10% of cases. As noted above, even in the presence of coronary artery atherosclerosis, IVUS has demonstrated that plaque rupture or intracoronary thrombosis is not seen. Once causative coronary occlusion has been excluded, ventriculography should be performed (unless a known contraindication exists, eg, chronic renal failure) to diagnose Takotsubo cardiomyopathy. The typical pattern of wall motion abnormality is the apical and midwall hypokinesia that earned this condition its original ‘takotsubo’ label, although atypical variants may occur (see above). After diagnostic cardiac catheterization, early access to high quality cardiac imaging is essential, in particular, echocardiography and, where available, CMR imaging, which can aid diagnosis in grey cases, assess potential complications, and exclude AMI.

Electrocardiogram

ST segment elevation is present in 80% of cases, which appears in the first 24 hours after the stressful trigger (if present), and onset of symptoms. The ST elevation is greatest in the precordial leads, but usually has a widespread pattern across the lateral and precordial leads. The ST elevation resolves approximately 24 to 36 hours after the onset of symptoms, changing into a widespread deep T wave inversion pattern that progressively deepens over the first few days. The changes are widespread, electrocardiographically involving multiple coronary artery territories. With the T wave inversion there is transient, reversible QTc prolongation, which can be very pronounced (>500 ms). This is rarely observed with STEMI due to coronary occlusion, and increases the risk for ventricular arrhythmias (in particular polymorphic ventricular tachycardia and torsades de pointes). The QTc can quickly return to normal, and this emphasizes the need for early imaging to identify the structural abnormalities before they resolve, to avoid making a mistaken diagnosis of inherited long QT syndrome and prescribing unnecessary therapy such as defibrillator implantation.

BIOMARKERS

Serum troponin levels, measured using standard assays, are positive in >95% cases. A striking feature is that the troponin level, although raised, is low compared with the extent of myocardial dysfunction. Conversely, the acute serum natriuretic peptide levels, when measured, are extremely high, and much higher than those observed during AMI. This different biomarker phenotype, with very high brain natriuretic peptide/N-terminal pro-brain natriuretic peptide (BNP/NTproBNP) and low troponin levels in Takotsubo cardiomyopathy cases vs high troponin and moderately raised BNP/NTproBNP with AMI cases, may be suggestive, but should be integrated into the clinical scenario and imaging given the nonspecific nature of the absolute biomarker values.
ECHOCARDIOGRAPHY

High quality cardiac imaging is important to confirm the diagnosis and screen for acute complications. Echocardiography is readily available in most modern cardiology units and aids diagnostic confirmation. Markedly reduced LV systolic function is the most prominent feature, alongside the characteristic pattern of wall motion abnormality, with the LV apex typically akinetic or markedly hypokinetic, and corresponding hypercontractility of the base. Citro et al reported the distribution of RWMA in 37 Takotsubo cardiomyopathy patients compared with 37 anterior STEMI-matched controls. Using the standard 17-segment model of the left ventricle from the American Society of Echocardiography classification, number of patients (n=37 per group) with hypokinesia (blue), akinesia (red), or dyskinesia (green) in each segment from basal (B), midventricular (C), or apical (D) levels of the left ventricle. Paired comparison of Takotsubo cardiomyopathy versus AMI patients is presented, with red asterisks identifying segments with significant differences between the patient cohorts.

Abbreviations: AMI, acute myocardial infarction; Ant-STEMI, anterior ST-elevation myocardial infarction; CX, circumflex artery; LAD, left anterior descending artery; RCA, right coronary artery; TTC, Takotsubo cardiomyopathy.

LV anatomy, they identified that the anterior basal segments (1 and 6) had preserved function in Takotsubo cardiomyopathy patients compared with AMI patients with anterior STEMI (Figure 7, page 87). Conversely, the inferior mid-LV and apical segments 8, 9, 10, and 14 (typical right coronary artery territory) were dysfunctional in Takotsubo cardiomyopathy patients, consistent with circumferential hypokinesia of the apical and mid-LV myocardium, but preserved in the AMI cases (Figure 7). More advanced echocardiographic techniques such as speckle tracking demonstrate a significant loss of apical torsion and ventricular systolic twist and twisting rate, which fully recovers at follow-up in Takotsubo cardiomyopathy patients, but remains perturbed in AMI controls.66

Echocardiography also has an important role to identify or exclude potential complications (Table IV). Assessment for LVOTO 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 LV apex.

<table>
<thead>
<tr>
<th>Table IV. Acute complications of Takotsubo cardiomyopathy.</th>
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<tr>
<td><strong>Abbreviations:</strong></td>
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<tr>
<td>LVOTO, left ventricular outflow tract obstruction;</td>
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<td>VT, VF, ventricular fibrillation;</td>
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<tr>
<td>VT, ventricular tachycardia.</td>
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<td><strong>Complication</strong></td>
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<td>LVOTO may be present</td>
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<td>Acute myocardial infarction</td>
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<td>Apical thrombus</td>
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<td>Pericarditis</td>
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<td>Ventricular wall rupture</td>
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<td>Pulmonary edema</td>
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<td>Cardiogenic shock</td>
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<tr>
<td>Left bundle branch block</td>
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<tr>
<td>Atrial fibrillation</td>
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<tr>
<td>VT, VF (4.8%)</td>
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<td>Death 1% to 2%</td>
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CARDIAC MAGNETIC RESONANCE

CMR in Takotsubo cardiomyopathy patients during the acute phase offers a number of advantages, if available.64 It offers advantages in the nongenetic patients and those where ventriculography was not performed. Given the apex is the most challenging part of the heart to image using echocardiography, it may clarify the extent and degree of apical dysfunction, and other anatomical variants when unusual patterns are observed during ventriculography or echocardiography, and exclude other forms of cardiac disease. The most helpful aspect of CMR is the use of late gadolinium enhancement (LGE) contrast imaging to exclude AMI. In most cases, LGE is completely absent both during the acute phase and at follow-up.65,66 In a few cases, patchy LGE during the acute phase has been reported, but was absent at follow-up.69,70 In a small subgroup of patients, a pattern of small, transmural LGE persists, and is observed in the ventricular apex at follow-up. In the absence of coronary atherosclerosis, and with the original hypokinesia during the acute phase involving a much wider myocardium volume, this is not a conventional myocardial infarction. This may reflect pressure-induced ischemia and myocardial necrosis due to the extremely high intraventricular pressures, which can be generated during acute stress, with the thin walled apex being the most susceptible, although postmortem histological confirmation of this LGE pattern is lacking. During the early phase of gadolinium contrast infusion, the presence of LV apical thrombus can be evaluated.

Finally, T2STIR studies can show increased regional water content, probably due to acute myocardial edema, although this has yet to be confirmed histologically. The increased T2STIR signal typically was colocalized with the areas of LV dysfunction (Figure 8), though this is less specific for Takotsubo cardiomyopathy and other forms of myocarditis should be considered and placed in the context of the clinical history. In most cases, all these abnormalities will have resolved by the follow-up scanning at 3 months.

In those patients with suspected STEMI, but normal coronaries, the ability to show characteristics of the myocardium using CMR provides an excellent technique for further assessment and differentiation of Takotsubo cardiomyopathy from other acute heart failure syndromes such as acute infective myocarditis.67 A disadvantage of CMR is the limited availability outside large centers, and a time lapse from presentation to scanning may allow some abnormalities to resolve before being fully appreciated.

TREATMENT

The acute dysfunction observed in Takotsubo cardiomyopathy is transient and reversible, and so the clinical strategy is to provide supportive care to sustain life and minimize complications until full recovery is achieved. In the mildest cases, no treatment may be necessary if recovery is rapid and uncomplicated, following the core medical principle of “first, do no harm.” Reviewing and removing multiple medications frequently initiated for patients with suspected ACS is a critical step for all patients with Takotsubo cardiomyopathy to ensure that they are not exposed to the risks of drugs for which there is no evidence that they will derive ben-
Takotsubo cardiomyopathy cases with evidence of heart failure may require a short course of medical therapy using evidence-based heart failure treatment (angiotensin-converting enzyme [ACE] inhibitors, β-blockers); in severe cases, consideration for mechanical support such as a ‘bridge to recovery’ may be necessary. Given that Takotsubo cardiomyopathy is a recently recognized entity, and individual centers and clinicians may see limited numbers of cases, there is still little evidence to base management strategies. Therefore, I will present my viewpoint in the context of the available data.

**Diagnosis and Initial Management**

In the initial phase, standard protocols for management of STEMI or NSTEMI should be followed until acute coronary occlusion has been excluded with cardiac catheterization. Ventriculography at the time of coronary angiography is essential (unless contraindicated due to known renal failure) and is often diagnostic in Takotsubo cardiomyopathy, and early access to high-quality cardiac imaging will demonstrate the LV dysfunction and characteristic pattern of wall motion abnormality. In some patients, LV function may normalize within 2 to 3 hours, which emphasizes the need for the rapid assessment. Although Takotsubo cardiomyopathy patients do not have STEMI secondary to coronary occlusion, they do have an acute heart failure syndrome with potential for acute complications. In my opinion, these patients should be admitted to an acute cardiac or medical unit with continuous cardiac ECG monitoring given the acute risk of arrhythmias, particularly in the setting of a significantly prolonged QTc interval. Correcting electrolyte disturbances and avoiding all QT-prolonging drugs will help minimize the risk of cardiac arrest during the acute phase. Noninvasive monitoring of hemodynamic parameters such as cardiac output, stroke volume, and peripheral vascular resistance may be helpful for continuous assessment of patient stability in the severe cases and evaluation of the hemodynamic consequences of pharmacological treatment. Contrast echocardiography and CMR with gadolinium will exclude LV thrombus in the early phase and provide further evidence to exclude myocardial infarction in the late phase. Once excluded, antiplatelets, anticoagulants, and statins can be reviewed for discontinuation. Systemic anticoagulation should be initiated if LV thrombus is confirmed.

**Mild Takotsubo cardiomyopathy cases**

Mild cases with rapid symptomatic improvement may not require therapy and may result in early discharge. Patients with persistent LV dysfunction for several days may benefit from conventional heart failure therapy with graded introduction of ACE inhibitors and β-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 (PVR), and if PVR is demonstrated to be significantly reduced then ACE inhibitors may be withheld. There is no clinical evidence for superiority of one specific drug over another, though studies in our animal models have suggested that carvedilol may have a beneficial effect above other β-blockers. β-blockers may also reduce the risk of cardiac rupture and counteract any residual elevated sympathetic drive.

**Severe Takotsubo cardiomyopathy cases with cardiogenic shock**

Takotsubo cardiomyopathy patients with severe hemodynamic instability provide unique challenges. Urgent echocardiographic assessment is essential to establish the degree of LV systolic impairment, to exclude contained ventricular rupture and cardiac tamponade, and identify the presence or absence of dynamic LVOTO.
If LVO TO is confirmed, systolic anterior movement of the anterior mitral valve leaflet with secondary mitral valve regurgitation may also be present. In the setting of LVO TO, β-blockers should be cautiously introduced to reduce the basal hypercontractility, prolong diastolic filling time, and increase LV end-diastolic volume, thereby reducing the LVO TO gradient and improving cardiac output. There is one report of the benefit of intravenous propranolol in two patients with Takotsubo cardiomyopathy and severe LVO TO. However, there are theoretical reasons to consider selecting carvedilol instead of propranolol in this scenario. In patients with LVO TO and low cardiac output, and/or those with low PVR, afterload reduction with intravenous nitrates and ACE inhibitors can be detrimental and should be avoided.

Currently, there is no evidence to support the use of an intra-aortic balloon pump (IABP) in patients with Takotsubo cardiomyopathy and cardiogenic shock, and there may be rationale against IABP use. This is reinforced by recent neutral data from the IABP-SHOCK II trial (Intra-aortic Balloon Pump in Cardiogenic SHOCK II) in a patient group with theoretically the most to benefit. A potential risk of IABP usage in Takotsubo cardiomyopathy is afterload reduction, which could induce or worsen dynamic LVO TO. In addition, patients with Takotsubo cardiomyopathy, normal coronary arteries, and low PVR are unlikely to derive benefit from IABP support.

The decision to use positive inotropic drugs in patients with cardiogenic shock secondary to Takotsubo cardiomyopathy is counterintuitive, but may be driven by an urgent clinical need and a lack of alternative options in many centers. Given its etiology and pathophysiology, further activation of myocardial β-adrenoreceptors or their downstream molecular pathways might worsen the LV dysfunction. In addition, dobutamine infusion may worsen dynamic LVO TO, and many cases of dobutamine-induced Takotsubo cardiomyopathy have been described during stress protocols. In contrast, levosimendan is a positive inotrope, which at low doses acts to sensitize cardiac myofilaments to calcium. In our Takotsubo cardiomyopathy animal model, levosimendan was shown to be an effective rescue from cardiogenic shock. A recent report also highlighted the potential use of levosimendan in a small cohort of Takotsubo cardiomyopathy patients. This open label, nonrandomized study without a control arm provides evidence of safety, and with the preclinical data, there is a potential scientific platform to consider a randomized clinical trial. In the interim, I would recommend levosimendan in preference to dobutamine, milrinone, or epinephrine for patients with Takotsubo cardiomyopathy complicated by severe cardiogenic shock. However, given the limited availability of levosimendan, physicians may be forced to resort to alternatives (eg, norepinephrine) as the only available inotrope until the patient can be transferred to a center with mechanical support options.

In patients with refractory cardiogenic shock and deteriorating multiorgan failure, it is appropriate to consider early referral for veno-arterial extra-corporeal membrane oxygenation (VA-ECMO) or for implantation of a left or biventricular assist device as a ‘bridge to recovery,’ given that the ventricular function of these patients has an excellent chance of a full recovery.

In the recovery phase, it is appropriate to introduce standard heart failure therapy including ACE inhibitors, β-blockers, and potentially an aldosterone receptor antagonist if the LVEF remains low for a prolonged period.

**LONG-TERM OUTCOME AND PROGNOSIS**

Patients who survive the acute catecholamine storm progressively recover, and normalize macroscopic features of ventricular function (ie, left ventricular ejection fraction) over the following days to weeks. The timing depends upon the severity of the acute episode. Mild cases may resolve within hours, whereas the most severe cases may have ventricular wall motion abnormalities persisting for several weeks after the initial episode before finally resolving. There is increasing evidence of physiological abnormalities persisting beyond the timeframe when resting contractile abnormalities have normalized ‘macroscopically.’ A clear example is the electrophysiological changes, such as a T wave inversion, which may take many months to resolve, and, in one case, the T wave inversion finally normalized between 9 and 12 months after the acute episode, whereas the left ventricular ejection fraction and RWMA had resolved by 3 months. A few studies have evaluated contractile reserve with cardiac stress at follow-up, and revealed persisting abnormalities in the timeframe reported. It is not known whether these were also present before the episode and reflect the potential for inducible apical dysfunction in a susceptible individual, or a resulting injury and dysfunction following the acute episode. The protocol used is also critical, given the evidence that dobutamine stress testing can trigger Takotsubo cardiomyopathy. Mechanistically, do the
Takotsubo cardiomyopathy patients recover LV function to normal and have a favorable prognosis compared with patients with full thickness infarction and the substrate for postinfarction heart failure and arrhythmias. However, fewer studies have compared Takotsubo cardiomyopathy patients with healthy age- and sex-matched controls who have not had an acute Takotsubo cardiomyopathy episode. In the studies published, there is a signal that long-term outcomes are poorer, although these studies are limited by cohort size, control group selection, and reported follow-up duration.

Currently, three conclusions and a fourth ‘viewpoint’ can be drawn regarding prognosis:

1. Prognosis in Takotsubo cardiomyopathy patients is significantly better compared with STEMI patients, reflecting the lower burden of atherosclerosis and post-MI heart failure. This is important to reassure both patients and their primary care physicians, and ensure that the diagnosis of AMI is removed from their medical records.

2. In patients with secondary Takotsubo cardiomyopathy, the triggering medical illness may have a major impact of prognosis in some cases, eg, significant neurological diseases, thyroid disease, or psychiatric disease.

3. If a patient has a recurrent episode of Takotsubo cardiomyopathy, they re-enter a high-risk phase due to the nature of complications during an acute episode of Takotsubo cardiomyopathy. The reported incidence of recurrence varies between 3.5% and 10% of cases from different series. Prognosis can be personalized to the individual patient in the context of the likelihood of recurrence.

4. Viewpoint: There is emerging evidence, not conclusive at this stage, of a slightly higher incidence of malignancy at follow-up in Takotsubo cardiomyopathy patients compared with controls. Whether this is real or a statistical artifact of control group selection remains to be determined, but, clinically, it is advisable to ask appropriate screening questions, particularly in patients without an overt identifiable stressful trigger.

**UNANSWERED QUESTIONS**

There are still many unanswered questions regarding the epidemiology, pathophysiology, complications, management, and long-term prognosis in Takotsubo cardiomyopathy. In this issue of *Dialogues in Cardiovascular Medicine*, we asked three experts to provide their opinion on some of these topics, to shed further light on the details, knowledge, and knowledge gaps in this field.
CONCLUSION

Takotsubo cardiomyopathy is a fascinating acute heart failure syndrome, now increasingly recognized by the medical community. Many facets of this condition remain to be understood or completely characterized, and current knowledge to guide optimal clinical practice is limited. To date, the majority of clinical reports are based upon relatively small cohorts and case series. The potential for national and international registries to prospectively collect larger numbers of patients should aid understanding of the epidemiology and natural history. This may provide the potential to organize networks to deliver appropriate research studies, and assess novel therapeutic strategies given the lack of current evidence-based treatments for patients with Takotsubo cardiomyopathy. This is a challenge given the number of cases at each center are ~5 to 15 per annum, and a broader network would be required to collect larger numbers.

Several countries have started to coordinate data collection in regional or national registries, and one international registry, the InterTAK registry (NCT01947621) has been launched to gather 10-year follow-up information on a large cohort of prospectively enrolled patients with confirmed Takotsubo cardiomyopathy. Under the umbrella of the Heart Failure Association of the European Society of Cardiology, a committee of experts is currently preparing a position statement using the currently available evidence to help practicing cardiologists and medical practitioners while awaiting evidence-based practice.

On reflection, Takotsubo cardiomyopathy is a humbling example of the fact that many facets of clinical cardiology and cardiovascular pathophysiology are still incompletely understood in the 21st century. Takotsubo cardiomyopathy has taught the medical community new approaches to cardiac physiology, and to question engrained beliefs within clinical practice.

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Takotsubo Cardiomyopathy

Expert Answers to Three Key Questions

1

Takotsubo cardiomyopathy: what is the epidemiological scale of the problem?

E. Bossone, R. Citro, F. Ferrara, J. A. Salerno-Uriarte

2

Takotsubo cardiomyopathy: is it a benign heart failure syndrome?

B. Schneider

3

Takotsubo cardiomyopathy: what current knowledge guides clinical management strategies?

E. Omerovic
Takotsubo cardiomyopathy; what is the epidemiological scale of the problem?

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Takotsubo cardiomyopathy (TTC) occurs mostly in postmenopausal women usually after a relevant emotional and/or physical stress. Male sex and advanced age (≥75 years) appear to be associated with higher rates of hospital complications and mortality. The concurrence of coronary artery disease is a common finding in many patients. The presence of a relevant coronary stenosis (≥50%) not supplying the dysfunctional myocardium is not an exclusion criterion for TTC. Despite the fact that in-hospital and long-term prognoses are generally favorable in the majority of cases, TTC may represent an important cause of sudden cardiac death. Further studies are needed to identify TTC patient cohorts at higher risk of complications and recurrences and to develop appropriate therapeutic strategies.

Keywords: apical ballooning; epidemiology; stress cardiomyopathy; Takotsubo cardiomyopathy

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HISTORICAL GLIMPSE

TTC was first described in Japan by Sato et al in 1990 and afterward it was reported by Dote et al in 1991. The historical term “takotsubo” was first coined on the basis of similarities between left ventriculography at the end systolic stage that was in the shape of a “takotsubo” fishing pot (round bottom and narrow neck) used in Japan to trap octopuses.

Since 1990, many studies and registries on TTC were increasingly reported in the world, which contributed to a better characteriza-

Table 1. Proposed criteria for TTC by the Mayo Clinic.

Abbreviations: ACS, acute coronary syndrome; TTC, Takotsubo cardiomyopathy.


* There are rare exceptions to these criteria such as those patients where the regional wall motion abnormality is limited to a single coronary territory. † It is possible that a patient with obstructive coronary atherosclerosis may also develop TTC. However, this is very rare in our experience and in the published literature, perhaps because such cases are misdiagnosed as an ACS. ‡ The diagnosis of TTC should be made with caution, and a clear stressful precipitating trigger must be sought.
tion of the disease in terms of demographic characteristics, clinical features, diagnostic approaches, and outcomes (Figure 1).2-4,6-24

**EPIDEMIOLOGY**

The current estimate of TTC prevalence is approximately 1% to 3% of patients undergoing coronary angiography (CA) due to a suspected acute coronary syndrome (ACS).1 TTC occurs mostly in postmenopausal women (in approximately 90% of cases) usually after strong emotional or physical stress.1 In the Nationwide Inpatient Sample (NIS-USA) discharge records for 2008, TTC was diagnosed in about 0.02% of all hospitalizations (6837 diagnosed with TTC out of 33,506,402 patients), mostly in elderly women (90% female; mean age ranging from 66 to 80 years), with a history of smoking, alcohol abuse, anxiety states, and hyperlipidemia. Women older than 55 have higher odds of developing TTC.20 Whites had a higher frequency of developing TTC when compared with African Americans or Hispanics (67.4% vs 4.4% and 4.3%, respectively).20 Moreover, data from the 2008-2009 NIS-USA showed that patients with TTC (24,701 patients) were more likely to have higher incomes than those with MI or orthopedic patients (P<0.0001).21

Interestingly, large registries have shown nonnegligible in-hospital mortality (0% to 8%) and long-term mortality (0% to 17%) along with a recurrence rate ranging from 0% to 11.4% (Table II).12-18,25-35 It should be also noted that data on prehospital sudden cardiac death (SCD) due to TTC are insufficient and are only limited to case reports.36-39

In this regard, a Japanese autopsy study of 91 SCD patients (77 male, 14 female) demonstrated that acute cardiac dysfunction related to stress...
### Table II. Takotsubo cardiomyopathy: overview of studies (≥30 cases) from 2000 to present.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Age (mean ±SD)</th>
<th>Patients/ female (%)</th>
<th>Region</th>
<th>TTC/ ACS (%)</th>
<th>TCC/ angiography (%)</th>
<th>In-hospital mortality</th>
<th>CV death (mean ±SD)</th>
<th>Follow-up months (mean ±SD)</th>
<th>Recurrences n(%)</th>
<th>Long-term mortality n(%)</th>
<th>CV death n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tsuchihashi et al</td>
<td>2001</td>
<td>67±13</td>
<td>88/76(86)</td>
<td>Japan</td>
<td>NR</td>
<td>NR</td>
<td>1(1)</td>
<td>NR</td>
<td>13±14</td>
<td>2/72(2.7)</td>
<td>1(1.3)</td>
<td>1(1.3)</td>
</tr>
<tr>
<td>Abdulla et al</td>
<td>2006</td>
<td>68±13</td>
<td>35/34(97)</td>
<td>Australia</td>
<td>2.6</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>6-66</td>
<td>4(11)*</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Hertting et al</td>
<td>2006</td>
<td>67±5</td>
<td>32/29(91)</td>
<td>Europe</td>
<td>NR</td>
<td>0.18</td>
<td>0</td>
<td>NR</td>
<td>6(2-30)</td>
<td>NR</td>
<td>2(6.2)</td>
<td>0</td>
</tr>
<tr>
<td>Eleesber et al</td>
<td>2007</td>
<td>66±13</td>
<td>100/95(95)</td>
<td>USA</td>
<td>NR</td>
<td>NR</td>
<td>2(1)</td>
<td>NR</td>
<td>26±12</td>
<td>10(11.4)</td>
<td>17(17)</td>
<td>7(7)</td>
</tr>
<tr>
<td>Kurowski et al</td>
<td>2007</td>
<td>72±9</td>
<td>35/33(94)</td>
<td>Europe</td>
<td>1.2</td>
<td>NR</td>
<td>3(8.6)</td>
<td>0</td>
<td>17±12</td>
<td>2(6)</td>
<td>0</td>
<td>NR</td>
</tr>
<tr>
<td>Burgdorf et al</td>
<td>2008</td>
<td>70±10</td>
<td>50/47(94)</td>
<td>Europe</td>
<td>NR</td>
<td>0.15</td>
<td>3(6)</td>
<td>NR</td>
<td>35±19</td>
<td>NR</td>
<td>6(12)</td>
<td>3(6)</td>
</tr>
<tr>
<td>Eshtehardi et al</td>
<td>2009</td>
<td>65±11</td>
<td>41/35(85)</td>
<td>Europe</td>
<td>1.7</td>
<td>0.3</td>
<td>0</td>
<td>NR</td>
<td>23±10</td>
<td>2(5)</td>
<td>1(2.4)</td>
<td>0</td>
</tr>
<tr>
<td>Regnante et al</td>
<td>2009</td>
<td>67±11</td>
<td>70/67(95)</td>
<td>USA</td>
<td>NR</td>
<td>0.4</td>
<td>1(1.4)</td>
<td>1(1.4)</td>
<td>12</td>
<td>2(2.9)</td>
<td>2(2.9)</td>
<td>0</td>
</tr>
<tr>
<td>Opolski et al</td>
<td>2010</td>
<td>67±11</td>
<td>31/29(93.5)</td>
<td>Europe</td>
<td>0.5</td>
<td>NR</td>
<td>0</td>
<td>NR</td>
<td>31.38±16.5</td>
<td>0(1.4)</td>
<td>0</td>
<td></td>
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<tr>
<td>Sharkey et al</td>
<td>2010</td>
<td>68±13</td>
<td>136/130(96)</td>
<td>USA</td>
<td>NR</td>
<td>NR</td>
<td>3(2)</td>
<td>NR</td>
<td>27.6±24</td>
<td>7(5)</td>
<td>17(12.5)</td>
<td>0</td>
</tr>
<tr>
<td>Schneider et al</td>
<td>2010</td>
<td>68±12</td>
<td>324/296(91)</td>
<td>Europe</td>
<td>NR</td>
<td>NR</td>
<td>7(2.2)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Parodi et al</td>
<td>2011</td>
<td>73±10</td>
<td>116/106(91)</td>
<td>Europe</td>
<td>2.9</td>
<td>NR</td>
<td>2(1.7)</td>
<td>1(0.8)</td>
<td>24±15.6</td>
<td>2(1.7)</td>
<td>11(9.6)</td>
<td>7(6)</td>
</tr>
<tr>
<td>Previtali et al</td>
<td>2011</td>
<td>67±11</td>
<td>132/125(98)</td>
<td>Europe</td>
<td>NR</td>
<td>NR</td>
<td>1(0.8)</td>
<td>3(1.1)</td>
<td>13</td>
<td>2(1.5)</td>
<td>1(0.7)</td>
<td>0</td>
</tr>
<tr>
<td>Eitel et al</td>
<td>2011</td>
<td>69±12</td>
<td>256/227(89)</td>
<td>Europe/North America</td>
<td>NR</td>
<td>NR</td>
<td>4(1.5)</td>
<td>NR</td>
<td>at 1 to 6</td>
<td>NR</td>
<td>4(1.6)</td>
<td>2(0.8)</td>
</tr>
<tr>
<td>Citro et al</td>
<td>2012</td>
<td>66±11.4</td>
<td>190/175(92)</td>
<td>Europe</td>
<td>NR</td>
<td>NR</td>
<td>5(2.8)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Samardhi et al</td>
<td>2012</td>
<td>64</td>
<td>52/51(98)</td>
<td>Australia</td>
<td>NR</td>
<td>NR</td>
<td>0</td>
<td>1(1%)</td>
<td>32.66</td>
<td>0(0)</td>
<td>0</td>
<td>NR</td>
</tr>
<tr>
<td>Looi et al</td>
<td>2012</td>
<td>65±11</td>
<td>100/95(95)</td>
<td>New Zealand</td>
<td>3.4(F)</td>
<td>NR</td>
<td>1(1%)</td>
<td>NR</td>
<td>36±20</td>
<td>7(7)</td>
<td>4(4)</td>
<td>0</td>
</tr>
<tr>
<td>Cacciotti et al</td>
<td>2012</td>
<td>71.9±9.6</td>
<td>75/73(97.3)</td>
<td>Europe</td>
<td>1.3</td>
<td>NR</td>
<td>0</td>
<td>NR</td>
<td>26.4±24</td>
<td>1(1.3)</td>
<td>2(2.6)</td>
<td>2(2.6)</td>
</tr>
<tr>
<td>Song et al</td>
<td>2013</td>
<td>59</td>
<td>137/101(74)</td>
<td>Korea</td>
<td>2.4</td>
<td>NR</td>
<td>0</td>
<td>NR</td>
<td>68.4</td>
<td>0</td>
<td>12(9)</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: ACS, acute coronary syndrome; CV, cardiovascular; MI, myocardial infarction; NR, not reported; TTC, Takotsubo cardiomyopathy.

*Higher rate of recurrent TTC in the group of TTC without apical sparing (4/21).

In this study overall mortality during follow-up did not differ significantly between both groups (ACS and TTC) for death in TC patients: hazard ratio [HR], 1.44; 95% confidence interval [CI], 0.52-3.95; P=0.39); however, of those patients who died, cardiac deaths were more frequent in patients with MI (100% vs 11% in patients with TTC, P<0.001).

In this study follow-up data were available in 23 patients (74.1%).
was an important cause of death in 19.8% of patients.40 A recent literature review of published cases reported a substantial number of life-threatening arrhythmias (3.4% of ventricular tachycardia or ventricular fibrillation) occurring in hospitalized TTC patients.41 Thus, TTC may represent an important cause of cardiac arrest.

Sex

TTC remains a syndrome that mainly occurs in postmenopausal women.1 In a German TTC registry (324 patients, 91% female and 9% male with a mean age of 68±12 vs 66±12 years, respectively), both sexes showed a similar clinical profile (age, symptoms, time from symptom onset to hospital admission)42; however, physical stress as the triggering event, shock and/or resuscitation on presentation, higher levels of cardiac biomarkers (troponin), and QT prolongation were more frequent in men.42 On the other hand, emotional stress or no identifiable trigger were more prevalent in women.42 Interestingly, the 2008-2009 NIS-USA reported 4.2% in-hospital mortality (24 701 TTC patients), and among these, >80% had underlying clinical illnesses, which were more frequent in males than in females (36.6% vs 26.8%, P<0.0001). Moreover, male patients had significantly higher total mortality rates than female patients (8.4% male vs 3.6% females, P<0.0001), which is likely related to the higher frequency of underlying critical illnesses.22 Thus, it appears that males may be considered to be at a higher risk for in-hospital complications and death.

Age

TTC predominantly occurs in elderly patients. The mean age ranges from 62 to 76 years with less than 10% of patients with TTC who are below the age of 50.1,43 In the Takotsubo Italian Network (TIN), TTC patients ≥65 years old have different clinical profiles that include a greater prevalence of hypertension, cerebrovascular disease, a lower glomerular filtration rate, and a lower LV ejection fraction (LVEF) at discharge compared with younger populations.18 Moreover, older adults (≥75 years) have higher in-hospital complications and in-hospital mortality rates (6.3% vs 2.8% rate of overall in-hospital mortality). On multivariate analysis, patients ≥75 (hazard ratio [HR], 2.45; 95% confidence interval [CI], 1.28-5.82; P=0.04) with LVEF on admission (HR, 0.874; 95% CI, 0.81-0.95; P<0.001) were the only independent predictors of...
adverse in-hospital events.\textsuperscript{18} It is evident that advanced age is associated with more frequent comorbidities and adverse outcomes.

**Stressors and comorbidities**

A stressful triggering event, either emotional or physical, is present in about two-thirds of cases; however, TTC may also occur in the absence of any identifiable preceding stressors.\textsuperscript{1,43} Emotional stressors may include death or severe illness/injury involving a family member, severe argument, or natural disasters. On the other hand, common acute medical illnesses (eg, respiratory, infectious, and neurologic diseases), postoperative state, and severe pain are the most common physical stressors (Table III).\textsuperscript{44}

Furthermore, the presence of severe comorbidities (eg, cerebrovascular accidents, drug abuse, anxiety disorders, mood disorders, malig-

<table>
<thead>
<tr>
<th>Frequency</th>
<th>OR (95% CI)</th>
<th>P value, McNemar Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>All TTC (n=24 701)</td>
<td>MI (n=25 069)</td>
<td>Orthopedic TTC vs MI Orthopedic TTC vs TTT TTC vs MI TTC vs Orthopedic</td>
</tr>
<tr>
<td>Charson Comorbidity Index score</td>
<td>1.4 (2.7%)</td>
<td>2.4 (3.2%)</td>
</tr>
<tr>
<td>Obesity</td>
<td>1494 (6.1%)</td>
<td>2930 (11.7%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14 434 (58.4%)</td>
<td>17 458 (69.6%)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>9261 (37.5%)</td>
<td>13 553 (54.1%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4661 (18.9%)</td>
<td>9282 (37.0%)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>11 013 (44.6%)</td>
<td>20 078 (80.1%)</td>
</tr>
<tr>
<td>Smoker</td>
<td>3290 (13.2%)</td>
<td>5487 (21.9%)</td>
</tr>
<tr>
<td>Asthma</td>
<td>2063 (8.4%)</td>
<td>1059 (4.2%)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>4615 (18.4%)</td>
<td>4035 (16.1%)</td>
</tr>
<tr>
<td>Pulmonary circulation disorder</td>
<td>1708 (6.9%)</td>
<td>941 (3.8%)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>152 (0.6%)</td>
<td>89 (0.4%)</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>20 (0.1%)</td>
<td>15 (0.1%)</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>223 (0.9%)</td>
<td>NA</td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>83 (0.3%)</td>
<td>35 (0.1%)</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>940 (3.8%)</td>
<td>523 (2.1%)</td>
</tr>
<tr>
<td>Drug abuse</td>
<td>862 (3.5%)</td>
<td>530 (2.1%)</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>860 (3.5%)</td>
<td>578 (2.3%)</td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>2204 (8.9%)</td>
<td>858 (3.4%)</td>
</tr>
<tr>
<td>Mood disorder</td>
<td>3696 (15.0%)</td>
<td>1815 (7.2%)</td>
</tr>
<tr>
<td>Delirium/dementia</td>
<td>1150 (4.7%)</td>
<td>1466 (5.9%)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>1704 (6.9%)</td>
<td>4251 (17.0%)</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>1105 (4.5%)</td>
<td>790 (3.2%)</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>282 (1.1%)</td>
<td>143 (0.6%)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1761 (7.1%)</td>
<td>618 (2.5%)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>3547 (14.4%)</td>
<td>2506 (10.0%)</td>
</tr>
</tbody>
</table>

Table IV. Analysis of the National Inpatient Sample from 2008 to 2009.

Abbreviations: CI, confidence interval; MI, myocardial infarction; NA, not available; OR, odds ratio; TTC, Takotsubo cardiomyopathy.


*In accord with the database user agreement for the National Inpatient Samples, we are not permitted to report patient numbers ≤10; in situations where ≤10 patients were found, we reported numbers as not available.
nancy, chronic liver disease, and sepsis) may also play an additive role in the complex pathophysiological mechanism of TTC. In this regard, TTC patients appear more likely to have asthma, chronic obstructive pulmonary disease, pulmonary circulation disorders, and hyperthyroidism compared with MI and orthopedic controls (Table IV, page 103). \(^{21}\)

**Coronary artery disease and TTC: a possible association**

Although normal coronary artery disease is frequently detected in TTC patients, several cases with angiographic CAD concurrence have been reported. \(^{45-49}\) In the 2008-2009 NIS-USA, CAD was present in 44.6% of the overall TTC population (24,701 patients), which is significantly higher than the orthopedic control population (17.4%). \(^{21}\)

Interestingly, in the German TTC registry, the evidence of coronary plaque (<50% stenosis) was more frequent in male patients than in female patients (82% vs 45% respectively; \(P<0.001\)) \(^{42}\)

Furthermore, among 450 patients (408 female, 91%; 42 male, 9%) enrolled in the Takotsubo Italian Network (TIN), 43 (9.6%) had at least 1 relevant coronary stenosis (>50%) not supplying the dysfunctional myocardium. \(^{49}\) It is important to note that the presence of significant CAD should not be considered an exclusion criteria for TTC. \(^{50}\) The meaning of this association is not clear considering that CAD does not seem to play a crucial role in the pathogenesis of TTC.

**Chronobiology insights**

A specific chronobiological pattern of TTC occurrence has been described in several studies, with most events occurring during the morning and summer (Figure 2). \(^{51,52}\) Moreover, a higher frequency of TTC onset on Monday has also been reported. \(^{11}\) It should be noted that if the higher morning frequency of TTC is similar to that of AMI, the summer preference is quite different because AMI is characterized by a higher winter peak incidence. \(^{53}\)

However, due to the limited number of studies and small sample size, no definite conclusions can be drawn about the chronobiological pattern of TTC. In the future, therapy could be tailored appropriately by the possible identification of the times when the patients are at the highest risk for TTC.

**CONCLUSION AND FUTURE DIRECTIONS**

TTC occurs mostly in postmenopausal women, usually after a relevant emotional and/or physical stress (Figures 3 and 4). \(^{12}\) Male sex and advanced age (≥75 years) appear to be associated with a higher rate of hospital complications and mortality. \(^{18,22,42}\) Younger women
have a greater burden of chronic psychological disorders and a predisposition to recurrences. The coexistence of CAD in TTC patients is common, probably due to the higher prevalence of cardiovascular risk factors in elderly postmenopausal women, but without a direct causal association. It is important to highlight that the presence of relevant coronary stenoses (≥50%) not supplying the dysfunctional myocardium should not be considered an exclusion criterion for TTC. Finally, further studies are needed in order to clarify the real impact of TTC on the etiology of SCD. It will also be important to identify specific TTC patient cohorts at a higher risk for complications and recurrences. In this regard, a more careful and appropriate management for the vulnerable population needs to be developed.

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Apical sparing in tako-tsubo cardiomyopathy.

Transient left ventricular apical ballooning in a community hospital in Germany.
*Int J Cardiol.* 2006;112:282-288.

Apical and midventricular transient left ventricular dysfunction syndrome (tako-tsubo cardiomyopathy): frequency, mechanisms, and prognosis.

Long-term prognosis of the transient left ventricular dysfunction syndrome (Tako-Tsubo cardiomyopathy): focus on malignancies.


Takotsubo cardiomyopathy (TTC) is a recently recognized heart failure syndrome with a clinical presentation resembling an acute coronary syndrome (ACS). Since left ventricular (LV) function returns to normal within a short period of time, TTC is normally regarded as a benign disease with a favorable prognosis. However, severe complications have been reported, mainly pulmonary edema, life threatening ventricular arrhythmias, atrial fibrillation, LV outflow tract obstruction, mitral regurgitation, mural thrombi resulting in stroke, cardiogenic shock, and death. Rare adverse events include pericardial tamponade, rupture of the LV free wall, and perforation of the interventricular septum. Patients with right ventricular involvement generally have a more severe clinical course. Close monitoring for early dangerous complications is advisable in TTC, which lasts at least 48 hours.

**Keywords:** acute coronary syndrome; apical ballooning; atrial fibrillation, cardiogenic shock; heart failure; left ventricular outflow tract obstruction; left ventricular thrombus; stroke; Takotsubo cardiomyopathy; ventricular tachycardia

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**Table 1. Potential complications of Takotsubo cardiomyopathy.**

<table>
<thead>
<tr>
<th>Category</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmias</td>
<td>• Ventricular tachycardia/fibrillation</td>
</tr>
<tr>
<td></td>
<td>• Atrial fibrillation</td>
</tr>
<tr>
<td></td>
<td>• Atrioventricular block</td>
</tr>
<tr>
<td></td>
<td>• Resuscitation</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>• Pulmonary edema</td>
</tr>
<tr>
<td></td>
<td>• Pleural effusion</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td></td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td></td>
</tr>
<tr>
<td>Intraventricular pressure gradient</td>
<td></td>
</tr>
<tr>
<td>Left ventricular thrombus formation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Stroke</td>
</tr>
<tr>
<td></td>
<td>• Peripheral embolism</td>
</tr>
<tr>
<td>Right ventricular involvement</td>
<td></td>
</tr>
<tr>
<td>Pericardial tamponade</td>
<td></td>
</tr>
<tr>
<td>Myocardial rupture</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Free wall rupture</td>
</tr>
<tr>
<td></td>
<td>• Perforation of the interventricular septum</td>
</tr>
<tr>
<td>Death</td>
<td></td>
</tr>
</tbody>
</table>

45% of the patients 6-10, 16-23 Independent predictors for the development of acute heart failure are advanced age, low left ventricular ejection fraction on presentation, higher admission and peak troponin levels, and a physical stressor preceding the onset of TTC.9 In the study by Madhavan et al, mechanical ventilation, inotropic support, and intra-aortic balloon pumping (IABP) had been required in a substantial number of cases (28%, 38%, and 17%, respectively).9 In some
patients, pulmonary edema due to acute LV dysfunction is aggravated by significant mitral regurgitation and/or LVOTO.

**Left ventricular outflow tract obstruction**

Due to myocardial stunning of the apical segments and hypercontraction of the basal LV myocardium, a dynamic intraventricular pressure gradient due to mitral valve systolic anterior motion may develop in the acute period of TTC (Figure 1). Significant left ventricular outflow tract obstruction (LVOTO) with gradients ranging from 20 to 140 mm Hg have been observed in 10% to 25% of patients presenting with TTC, often accompanied by mitral regurgitation. Abnormal Q waves in the electrocardiogram, hypotension, and cardiogenic shock are more frequent in these patients. Use of inotropic drugs or nitrates may aggravate LVOTO whereas β-blocker treatment with propranolol has been shown to decrease the gradient. Normally, the outflow tract obstruction resolves spontaneously over a few days.

**Mitrval regurgitation**

Acute mitral regurgitation is another potentially serious complication of TTC occurring in 14% to 25% of patients. Left ventricular ejection fraction is lower and pulmonary artery pressure is higher in cases of significant mitral regurgitation, and these patients present more often with acute heart failure or cardiogenic shock. Two independent mechanisms with differing pathophysiology may cause acute mitral regurgitation: (i) systolic anterior motion of the mitral valve in association with dynamic LVOTO; and (ii) apical tethering of the mitral valve apparatus. In most patients, early improvement of acute mitral regurgitation can be observed in conjunction with normalization of LV function, which may, however, be somewhat delayed compared with patients without acute mitral regurgitation.

**Cardiogenic shock**

Cardiogenic shock has been observed in up to 46% of patients with TTC. In more recently published studies reporting on over 50 patients, the prevalence of cardiogenic shock is lower; ranging from 6% to 20%. Cardiogenic shock, primarily due to acute LV dysfunction, may be aggravated by right ventricular involvement, LVOTO, or acute mitral regurgitation. Repeat echocardiography (ECG) plays an important role in determining the exact mechanism of cardiogenic shock in each patient in order to apply an appropriate therapy. The mortality of cardiogenic shock in TTC is high (between 17% and 30%), but appears to be lower than the reported 40% to 62% mortality in reperfused ST-elevation myocardial

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**Selected Abbreviations and Acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS</td>
<td>acute coronary syndrome</td>
</tr>
<tr>
<td>CMRI</td>
<td>cardiac magnetic resonance imaging</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram, electrocardiographic</td>
</tr>
<tr>
<td>LV</td>
<td>left ventricular</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>non-ST elevation myocardial infarction</td>
</tr>
<tr>
<td>STEMI</td>
<td>ST-elevation myocardial infarction</td>
</tr>
<tr>
<td>TTC</td>
<td>Takotsubo cardiomyopathy</td>
</tr>
</tbody>
</table>
infarction (STEMI). This may be due to the early spontaneous reversibility of LV dysfunction in TTC.

**Arrhythmias**

New onset of atrial fibrillation has been reported in 5% to 15% of patients with TTC. Since this arrhythmia further reduces cardiac output, heart failure is often associated with the onset of atrial fibrillation. During the acute phase of TTC, ventricular arrhythmias occur in 4% to 9% of patients. Resuscitation because of cardiac arrest, which may be the initial presenting symptom, has been reported in 4% to 6% of the cases. In rare instances, ventricular arrhythmias have been documented weeks after manifestation of TTC when LV function had already normalized. Bradycardia due to atrioventricular block and asystole have been described in a limited number of patients with TTC (2% to 5%).

**Thrombus formation**

Thrombus formation may be detected within the akinetic ventricular apex in 2% to 8% of patients (Figure 3), which frequently results in stroke or arterial embolism. Patients with thrombus formation present later in the clinical course as indicated by the higher frequency of negative T waves on the admission ECG. Best visualized by CMRI, most thrombi develop between day 2 and day 5 after symptom onset when LV function is still depressed. However, new thrombus formation and subsequent embolism has been described 14 days after symptom onset when the left ventricle had already regained normal systolic function.

**Pericardial effusion**

Acute pericarditis with recurrent chest pain, reappearance of ST-segment elevation, and a small amount of pericardial effusion has been observed in some patients during the recovery phase of TTC. By performing CMRI early after admission, mild pericardial effusion may be detected in up to 43% of the patients. Pericardial tamponade requiring pericardiocentesis is rare and has so far been described in single case reports.

**Ventricular wall rupture**

Mechanical complications including rupture of the ventricular free wall or perforation of the interventricular septum are observed in less than 1% of cases. The ECG frequently shows Q-waves and persistent ST-segment elevation before rupture occurs, usually between day 2 and day 8 after symptom onset. A high outflow tract gradient may favor left ventricular free wall rupture. One case of right ventricular rupture has also been described. Rarely, perforation of the interventricular septum occurs and may be successfully treated by surgery.

**Mortality**

Initial small case series have reported a mortality rate of 6% to 12%. This may be explained by the fact that some patients suffered from a severe underlying disease that triggered the TTC and was the primary reason for death. In large studies and registries, inhospital mortality is low and has been observed in 1% to 3% of the cases.
patients with TTC, mainly caused by refractory cardiogenic shock or ventricular fibrillation.\(^{1,8,9,17,22}\)

**LONG-TERM PROGNOSIS**

A recurrence rate of 5% to 10% has been reported during the five years following the initial event.\(^{17}\) Survival at 3 years is significantly reduced when compared with an age- and sex-matched general population. Excess mortality predominantly occurs in the first year after diagnosis and is usually caused by a noncardiac illness such as malignancy.\(^{17}\)

**CONCLUSION**

Although clinical symptoms are more subtle in TTC compared with acute myocardial infarction\(^6\) and the rise of cardiac markers is less pronounced,\(^{14}\) adverse events may develop in up to 50% of the patients with TTC. Close monitoring for early dangerous complications is advisable and should last for at least 48 hours as is done for patients with ACS. Daily ECG’s and repeated echocardiograms should be obtained.

Patients with persisting ST-segment elevation and biventricular involvement require special attention as they may be at a higher risk for severe complications including myocardial rupture and thrombus formation.\(^{5,7,11,36,37}\) The poor outcome of patients with left ventricular thrombi and systemic embolism suggests that all TTC patients should receive anticoagulant treatment as long as LV akinesia persists. TTC has to be regarded as a clinical entity with a potentially complicated clinical course similar to patients with STEMI and NSTEMI.

**REFERENCES**


Takotsubo cardiomypathy: what current knowledge guides clinical management strategies?

Elmir Omerovic, MD, PhD

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Department of Cardiology - Sahlgrenska University Hospital - Gothenburg - SWEDEN

Takotsubo syndrome (TS) is characterized by a severe, but reversible left ventricular wall motion abnormality without an explanatory coronary lesion. An increasing number of patients are diagnosed with TS worldwide and current guidelines from the European Society of Cardiology and American Heart Association/American College of Cardiology organizations do not provide treatment recommendations for TS. The fact that TS is usually self-healing and, due to the high risk of complications, treatment is challenging and should be based on the primum nil nocere (“first, do no harm”) principle. In mild cases, no treatment or limited anticoagulation therapy may be sufficient. Positive inotropic and vasodilating agents should be avoided. In severe cases, early treatment using venoarterial extracorporeal membrane oxygenation or a left ventricular assist device should be considered.

At our clinic, at the Sahlgrenska University Hospital in Gothenburg, we diagnose and treat on average 3 to 5 TS patients per month—a rate that has been constant over the last couple of years. The discussion in this paper is based on clinical experience, our opinion, and available experimental and clinical evidence in the literature.

**Keywords:** extracorporeal membrane oxygenation; left ventricular tract obstruction; peripheral vascular resistance; Takotsubo syndrome

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**SELECTED ABBREVIATIONS AND ACRONYMS**

<table>
<thead>
<tr>
<th>ACRONYM</th>
<th>DEFINITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>cAMP</td>
<td>cyclic adenosine monophosphate</td>
</tr>
<tr>
<td>ECMO</td>
<td>extracorporeal membrane oxygenation</td>
</tr>
<tr>
<td>IABP</td>
<td>intra-aortic balloon pump</td>
</tr>
<tr>
<td>LV</td>
<td>left ventricle</td>
</tr>
<tr>
<td>LVOTO</td>
<td>left ventricular tract obstruction</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>PVR</td>
<td>peripheral vascular resistance</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
</tr>
<tr>
<td>TS</td>
<td>Takotsubo syndrome</td>
</tr>
</tbody>
</table>

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**GENERAL TAKOTSUBO SYNDROME CONSIDERATIONS AND TREATMENT OPTIONS**

One of the most important criteria for diagnosis of TS is evental spontaneous restoration of normal cardiac function through the process of self-healing. Accordingly, the major objective of in-hospital treatment should be supportive care to sustain life and minimize compli-
cations during recovery (Figure 1). In mild cases, either no treatment or a short course of limited medical therapy may be sufficient. In severe cases that are complicated by progressive circulatory failure, the patients should be considered for early mechanical support as a “bridge to recovery.” Before we discuss the specific details of optimal treatment strategies, it may be appropriate to provide a short review on the current knowledge relevant to the clinical management of TS.

The most characteristic hallmark of the syndrome is a development of a peculiar type of reversible left ventricular dysfunction with extensive akinesia affecting two-thirds of apical segments. This leads to cardiac dysfunction that may progress, in predisposed patients (due to the natural course of the syndrome or as a consequence of iatrogenic damage), to fulminant heart failure, cardiogenic shock, and, literally, heart rupture, leading to death. Despite the presence of dramatic contractile dysfunction and the severity of signs and symptoms during the acute phase, TS is a transient disorder in the majority of patients. It was initially believed that TS was a benign syndrome, however, today substantial evidence suggests that TS is associated with a considerable risk of severe complications and death. Indeed, this risk is approaching that reported in patients with acute coronary syndromes. The most feared complications in the acute phase include malignant ventricular arrhythmias, thromboembolic complications (e.g., stroke, pulmonary embolism), and worsening heart failure leading to cardiogenic shock, all of which may result in loss of life or a permanent handicap. What we know regarding the disease mechanism, based on preclinical and clinical observations, is that intensive catecholamine overstimulation of the myocardium may be responsible for the development of myocardial dysfunction. What we do not know is how TS affects prognosis, what the optimal treatment is, which mechanisms are involved in the development of cardiac dysfunction, and which pathways are responsible for effective healing. The reason for the “late” recognition of TS in contemporary medicine is probably multifactorial. First, the initial clinical course of takotsubo is indistinguishable from myocardial infarction. Second, the well-known phenomenon of gender disparity in diagnostics, treatment, and participation in clinical trials might have contributed to the delay because TS mostly affects women. Third, TS may be a genuinely new disease entity that was either not present or not so prevalent in the past.

**NEW CLINICAL OBSERVATIONS IN TAKOTSUBO SYNDROME: IMPORTANCE FOR TREATMENT DECISIONS**

Important new observations about clinical manifestations of TS have emerged that are of general importance. It is not unusual for a TS patient to survive an episode in which myocardial akinesia involves >60% of the left ventricle (LV). In the setting of acute myocardial infarction, loss of function of that magnitude would most likely result in rapid death. Such a contradictory finding highlights the enigmatic nature of TS and the importance of a cautious approach in the process of clinical decision-making. How can it be that the majority of TS patients are hemodynamically stable at rest despite the presence of such an extensive contractile dysfunction? In order to address this question, we hypothesized that TS is a cardiocirculatory syndrome. In other words,
compensatory cardiocirculatory mechanisms are activated to maintain sufficient perfusion of the vital organs in the setting of TS. Indeed, we have demonstrated that TS is associated with decreased sympathetic tone, decreased peripheral vascular resistance (PVR), and preserved cardiac output despite extensive apical akinesia. These findings differ from those observed in acute myocardial infarction and are consistent with our observation of near-normal filling pressures in TS (unpublished observations). When compared with acute heart failure due to extensive ischemic damage, this is yet another counterintuitive finding. Indeed, if one considers that TS is associated with highly elevated plasma levels of catecholamines, it may be reasonable to view TS as a condition that is interrelated with both cardiac and extracardiac alterations. In addition to its unique cardiocirculatory profile, TS may be intimately linked to other organ systems. These details suggest an important “knowledge gap” in our understanding of cardiovascular physiology, in general, and of TS, in particular. In our opinion, it is the combination of the undeniable “knowledge gap,” the fact that TS, in most cases, is self-healing, and the presence of a substantial risk of death that calls for the respect of the fundamental ethical principle *primum nil nocere* (“first, do no harm”) when considering treatment options in patients with TS.

**Initial patient care**

In the initial phase, standard protocols for the management of patients with acute coronary syndrome should be followed until this diagnosis has been convincingly excluded. This is achieved by means of urgent cardiac catheterization, which demonstrates that coronary anatomy and coronary flow cannot reasonably explain the severity or extent of segmental LV dysfunction. Ventriculography, at the time of coronary angiography, is essential and often diagnostic in TS. It also reveals other “atypical forms” of TS such as reversed, midventricular, and regional forms, ie, inferior, anterior, lateral, and apical (and their combinations). Similarly, an early transthoracic echocardiogram will noninvasively demonstrate and document wall motion abnormalities. In some patients, LV function may normalize within 2 to 3 hours (our unpublished observations), which strengthens the need for the early assessment of LV function in order to not miss the diagnosis. Given the risk of arrhythmias, patients should be admitted to an acute cardiac or medical unit with continuous electrocardiogram monitoring, particularly in the setting of a prolonged QTc interval, which is present in a substantial number of TS patients. Noninvasive monitoring of hemodynamic parameters such as cardiac output, stroke volume, and PVR, for example, with impedance electrocardiography, may be helpful in the continuous assessment of patient stability and evaluation of the hemodynamic consequences of pharmacological treatment. Contrast echocardiography and magnetic resonance imaging (MRI) of the heart in the early phase will exclude LV thrombus and provide further evidence to exclude myocardial infarction.

**Pharmacological therapy**

Once diagnosed with TS, therapy is based upon the patient’s overall clinical condition. It is important to realize that there are no randomized controlled trials (RCTs) to help define the optimal medical treatment or provide a base for our recommendations. Consequently, there is a large heterogeneity in opinions concerning the best treatment for TS worldwide. Many authors advocate extrapolation of the general knowledge acquired in the field of heart failure, and recommend the use of standard medications such as angiotensin-converting enzyme (ACE) inhibitors, β-blockers, and diuretics. Aspirin is also suggested for use in the presence of coexisting coronary atherosclerosis. At our hospital, we do not initiate treatment with β-blockers and ACE inhibitors in the acute phase, respecting the “*do no harm*” principle. After normalization (or near-normalization) of segmental function and hemodynamic status, we initiate a long-term treatment (arbitrarily continued for one year) with β-blockers in the absence of contraindications or intolerance, which is based on the observation that the condition may recur in ~15% of patients. In the absence of data from RCTs, the appropriate duration of any therapy for TS is unknown.

**PHARMACODYNAMIC CONSIDERATIONS FOR THE TREATMENT OF TAKOTSUBO SYNDROME**

Based on the current evidence implicating catecholamine toxicity in the pathophysiology of TS, the blockade of adrenergic receptors may be a suitable treatment option. However, whether adrenergic blockade is beneficial, neutral, or deleterious is unknown. Some experimental data support the use of β-blockers in TS. Metoprolol improved the LV ejection fraction in primates with adrenaline-induced TS within 24 hours. However, cardiac dysfunction also normalized in animals who received no treatment. Although a number of studies were conducted to investigate drug treatment of TS in humans, there are no RCTs, which limit the reliability of current evidence derived primarily.
from observational studies. A few reports have demonstrated the benefits of β-blocker use, particularly in the presence of dynamic left ventricular tricular obstruction (LVOTO). Treatment with β-blockers may also protect against malignant arrhythmias that occur in a substantial number of TS patients. Some patients appear to be prone to development of TS after withdrawal of β-blockade, which supports the hypothesis that β-blockers could prevent TS. β-blockers may theoretically reduce the risk of cardiac rupture in TS. There is no clinical evidence suggesting the superiority of one specific treatment over another. Some studies in a small-animal model suggest that carvedilol (a nonselective β- and α; blocker) may have a beneficial effect that is greater than that of other β-blockers. Regrettably, other data suggest that β-blockers may not be protective at all. For example, as many as 20% of TS cases occur in patients already receiving β-blocker treatment. Some small retrospective studies have compared patients treated with traditional cardioprotective medications including β-blockers, ACE inhibitors, calcium channel blockers, or aspirin with controls. There was no difference in LV function at admission or at follow-up, suggesting the ineffectiveness of standard heart failure medications in the prevention and treatment of TS. All this information strengthens the application of the “do no harm” principle. Therefore, in our judgment, for safety reasons, it is prudent not to extrapolate treatment algorithms from heart failure and administer pharmacological agents such as calcium channel blockers, β-blockers, and ACE inhibitors to TS patients. We should wait until we achieve a better understanding of the pathophysiology behind TS and until we acquire knowledge from properly designed and conducted RCTs.

**Mild cases**

Mild cases with rapid symptomatic improvement need no therapy and early discharge is possible. Some authors advocate conventional heart failure therapy with graded introduction of ACE inhibitors and β-blockers licensed for heart failure. However, there is evidence that a substantial proportion of TS patients may have altered peripheral sympathetic nerve activity associated with low PVR. Therefore, administration of ACE inhibitors, β-blockers, calcium channel blockers, or other vasoactive drugs may be harmful. The safety and efficacy of these pharmacological agents in the treatment of patients with TS have not been established.

**Severe cases and cardiogenic shock**

A substantial number of patients with TS may present with low BP but have normal or near-normal cardiac output. It is, therefore, important to provide objective evidence of worsening hemodynamic status (ie, decreasing cardiac output or cardiac index) before making a decision about pharmacological treatment. TS with severe hemodynamic instability creates unique challenges. The likelihood of acute heart failure and worsening clinical status increases in the presence of the following three variables: age >70 years, presence of a physical stressor, and LV ejection fraction <40 percent. TS complicated by cardiogenic shock is reported in 15% to 20%, pulmonary edema in 20%, ventricular tachycardia in 4%, and death in 5% of patients. In TS patients with a compromised hemodynamic status, urgent cardiac catheterization with ventriculography or echocardiographic assessment is essential to establish the degree of LV systolic impairment, and, vitally, to determine the presence or absence of LVOTO. Almost 25% of TS patients develop LVOTO and treatment of these patients is particularly complicated. The presence of LVOTO may already be recognized at the time of cardiac catheterization and angiography by a catheter pullback across the aortic valve. Some authors recommend cautious treatment with β-blockers in the presence of dynamic LVOTO based on the rationale that prolongation of diastolic filling time and an increase in LV end-diastolic volume reduces the LVOTO gradient and improves cardiac output. Electrical pacing of the right ventricular apex could be considered, if we apply the same reasoning as in the treatment of obstructive cardiomyopathy.

**Positive inotropic agents**

The decision to use sympathomimetic drugs for positive inotropy is challenging and counterintuitive in TS. Given what is known about the mechanisms involved in TS, further activation of catecholamine receptors or their downstream molecular pathways might worsen patients’ clinical status and prognosis. Therefore, the use of inotropes such as dobutamine, noradrenaline, dopamine, adrenaline, milrinone, and isoprenaline should be generally regarded as contraindicated in TS. There is solid evidence that catecholamines can directly induce TS, worsen LVOTO by further increasing hypercontractility of the midventricular segment, and delay spontaneous recovery in humans. Similarly, administration of adrenaline and isoprenaline induces a TS-like condition in rats and mice. The use of the novel inotrope levosimendan in conjunction with noradrenaline has previously been described in patients and in an experimental rat model. The mode of action of levosimendan is differ-
ent from that of standard inotropes because it does not act on adrenergic receptors, but rather exerts its positive inotropic effects by prolonging the interaction between actin and myosin. However, this suggestion should be taken cautiously because levosimendan has been shown, in experimental models, to have an adrenergic-like activity because it inhibits phosphodiesterase, which, therefore, leads to increased levels of intracellular cyclic adenosine monophosphate (cAMP).

Furthermore, levosimendan has a pronounced dose-dependent vasodilatory effect, which may further compromise the hemodynamic status in an unstable TS patient with low PVR. Similarly, in cases where the low cardiac output is associated with low PVR, afterload reduction with intravenous nitrates and ACE inhibitors can be detrimental and should not be used.

**Mechanical support**

Intra-aortic balloon pump (IABP) is recommended by some authors for cardiogenic shock due to TS. IABP improves cardiac output largely through afterload reduction, and this nonpharmacological therapy has been in use for the treatment of cardiogenic shock for several decades. However, in light of recent neutral data from the IABP-SHOCK II trial and the fact that IABP may worsen dynamic LVOTO (Figure 2), we advise against IABP in unstable TS patients. Instead, we advise that patients presenting with worsening hemodynamics, rapid progression to cardiogenic shock, and deteriorating multiorgan failure should be considered for veno-arterial extracorporeal membrane oxygenation (ECMO) or implantation of a left or biventricular assist device as a "bridge to recovery," given that the ventricular function of these patients has an excellent chance of full recovery.

**Prevention of thromboembolism**

TS may be associated with blood hypercoagulability. Indeed, we often encounter thromboembolism in our patients, which might reflect the vasoconstrictor, platelet activation, or prothrombotic effects of high catecholamine levels. In our practice, we diagnose thromboembolism in ~4% of TS patients, which suggests that the potential risk of intraventricular thrombus formation and systemic embolization should be addressed. In our opinion, administration of low-molecular-weight heparin (LMWH), aspirin, and/or P2Y12 receptor antagonists such as clopidogrel, prasugrel, or ticagrelor should be a part of the standard treatment and it should be initiated early. Echocardiography and cardiac MRI will provide important information about the presence of mural thrombus and the extent of wall motion abnormalities. However, data to ascertain suitable criteria for use of anticoagulation to prevent thromboembolism in patients with TS are scarce. Indirect evidence from randomized trials on anticoagulation for the prevention of LV thrombus formation in myocardial infarction patients has shown that the use of anticoagulation treatment for 10 days reduces the incidence of LV thrombus formation. The use of anticoagulation therapy in patients with known LV thrombus is...

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**Figure 2.** Continuous Doppler recording at the level of LVOT in patients with Takotsubo syndrome during IABP.

A 64-year-old woman presented with sudden central chest pain, dizziness, and ST-elevation in anterior leads. The patient was hypotensive on arrival to the catheterization lab with a systolic blood pressure ~80 to 90 mm Hg. Coronary angiography showed significant stenosis in one minor diagonal branch, but with normal flow in all coronary arteries. Ventriculography showed typical apical ballooning that was engaging ~60% of the left ventricle. On suspicion of cardiogenic shock based on sustained hypotension, the patient received IABP immediately after angiography. The patient's condition deteriorated immediately after administration of IABP, with worsening hypotension. ECG showed increasing peak pressure gradient (arrows) in the LVOT and decreasing stroke volume with every assisted (4:1) beat. The IABP was removed and stroke volume increased immediately to near-normal values. The patient recovered over the next few days without any pharmacological treatment other than aspirin and fondaparinux. This case illustrates the danger of iatrogenic injury and violation of the “do no harm” principle.

**Abbreviations:** ECG, echocardiography; IABP, intra-aorta balloon pump; LVOT, left ventricular outflow tract.
supported by observational studies in which this therapy, which was administered over a period of four to six months, was associated with a reduction in the rate of embolization. We recommend approximately three months of anticoagulation treatment if an intraventricular thrombus is detected. For patients without thrombus, but with severe left ventricular dysfunction, we suggest anticoagulation treatment until widespread LV akinesia substantially improves or for three months, whichever is shorter. It is controversial whether anticoagulation treatment is advisable because there is a possibility of TS being complicated by cardiac rupture. However, the reported number of cases complicated by heart rupture is rather low compared with the number of cases showing an LV thrombus.

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My children look at me in disbelief when I say that when I was a boy there were no earthquakes. They accept them as a normal part of life now. A generation of Christchurch children now knows that you do not build your house on untrustworthy land, that you cannot predict the future, and that nature exerts the greatest of forces. In the end, Christchurch got off lightly. The death toll could have been so much worse. The central city is lost, but we are a first world country with resources to cope. Rebuilding a century of buildings will take decades and will be dependent on our economic fortunes. However, we will come through it. Many disasters that are more serious have struck societies less well equipped to cope. The February earthquake was surreal. Suddenly, our city was a third world disaster zone, the likes of which you only see on TV. The roads were suddenly potholed, flooded, and jammed with people leaving.

There was no power or communication. The wounded were making their way to the hospital. Dazed people were wandering the streets without purpose. You had no way of knowing if your children were alive—you just had to trust. My wife and I stayed at the hospital and worked. We could not have gotten home anyway—Paul Bridgman.

**GEOLOGY, QUAKES, AND CONSEQUENCES**

Two major earthquakes occurring six months apart struck the city of Christchurch. The first was in September 2010 and the second was in February 2011. The September earthquake was a magnitude of 7.1 and struck at 4:36 AM. It was shallow and centered under farmland 40 kilometers west of Christchurch City. Significant damage occurred in rural areas and in older buildings across Christchurch City (Figure 1, and Figure 2 page 122). Insurance claims for the earthquake are confirmed as being close to 3.5 billion NZD.

It was the second earthquake that occurred on February 22, 2011 at 12:51 PM that caused the most death and destruction. While it was smaller and
technically an aftershock of the first earthquake, it was situated near the city center and was at a very shallow depth. This, and the peculiarities of the energy wave generated, resulted in a peak ground acceleration in central Christchurch of over 1.8g. This was extremely damaging to the buildings of the city center (Figures 3 to 5). Effectively, the buildings were thrown a meter up into the air and then as they were coming down, the ground came back up to hit them. 185 people died and the estimated cost is currently 40 billion NZD. It is reputedly the world’s biggest insurance event. Over half of the deaths occurred in the six

Figure 2. Cracked road, September 2010. © David Alexander/AP/SIPA.

Figure 3. Dust rises in the city center during the earthquake, February 2011. © Brett Phibbs/AP/SIPA

Figure 4. Leaning buildings, February 2011. © Photo by Craig Greenhill/Newspix/Rex Features

Figure 5. Injury sustained, February 2011. Photo by Ian McGregor/The Press. © Fairfax New Zealand Limited.
story Canterbury Television building that collapsed and caught fire. The majority of the rest of the center city stayed standing, but damage to the building’s foundations subsequently resulted in 1000 city center buildings that had to be demolished (Figures 4 and 5).

Both major earthquakes generated their own series of aftershocks that further damaged buildings. With schools shut and aftershocks taking a heavy psychological toll on the population, tens of thousands of people moved away from Christchurch for weeks after each major event. Fortuitously, Christchurch Hospital was able to stay operational following both events. In the case of the second earthquake, the hospital buildings were the only multistory buildings in Christchurch to survive in a state fit for use.

**PSYCHOLOGY**

The first earthquake presented an obvious opportunity to study patients with chest pains precipitated by emotional stress. Christchurch Hospital, the city’s only acute hospital, remained functional, and, in the days that followed, acute cardiology-admitting staff quickly noted a large number of admissions with chest pain precipitated by the earthquake. This enabled a prospective log of postearthquake patients with chest pain to be maintained. Their final diagnoses included noncardiac chest pain, myocardial infarction (MI), and stress cardiomyopathy. We set strict diagnostic criteria for these three conditions and this yielded a final study population of 17 women, 6 with stress cardiomyopathy, 5 with MI, and 6 with noncardiac chest pain. The patients returned as outpatients for a semistructured interview with the senior clinical psychologist who was blind to the cardiology diagnosis. Particular strengths of our study included: (i) binding to the cardiology diagnosis; (ii) the homogenous nature of the patient groups; and (iii) the ability to standardize the interviews. Our major finding was that the women presenting with noncardiac chest pain scored high for anxiety traits, whereas the other two groups were more normal. Patients presenting with noncardiac chest pain often had a history of anxiety disorder, greater generalized and health-related anxiety, and scored highest for neuroticism traits (Table 1). In contrast, the women with stress cardiomyopathy were the most psychologically robust. Psychiatric histories and scores for depression were the same across all three of our groups. Our finding of increased anxiety in the noncardiac patients is consistent with previous reports showing it to be strongly associated with the presence of anxiety disorders. However, our findings in the stress cardiomyopathy patients are quite different from previous reports that found increased anxiety in these patients. Those studies were, however, unblinded studies on women also can develop stress cardiomyopathy, and it was shown that noncardiac chest pain is clustered in women with increased anxiety.

### COMPARING EARTHQUAKES

Within fifteen minutes of the February earthquake, trauma cases started arriving in the emergency department (ED). Within an hour, the ED was full and chest pain patients started to arrive. The acute cardiology team of the day cared for the admissions and again ran a prospective log of chest pain presentations. The rest of us discharged as many patients as we could. The hospital was running on patchy emergency power generation and was flooded in many areas from broken pipes in the walls and ceilings. An audit was commenced after the September earthquake to fully document the pattern of cardiac admissions. Clinical notes and electronic discharge 

| Table 1. Evaluation of anxiety and depression in patients presenting with chest pain. |
|---------------------------------------------|---|---|---|
| HADS Anxiety                               | 8.2 (2-15) | 6.6 (4-9) | 5.3 (0-12) |
| HADS Depression                            | 3.3 (0-9)  | 3.4 (0-8) | 2.3 (1-6)  |
| HAQ                                         | 13 (3-28)  | 14 (11-16) | 7 (1-17) |
| EPO-BV neuroticism                         | 34 (18-51)| 26 (22-33) | 25 (15-36) |
| EPO-BV extraversion                        | 35 (21-42)| 32 (30-37) | 33 (23-46) |
| IES-R                                       | 38 (3-74) | 31 (7-67) | 27 (15-47) |

Abbreviations: CP, chest pain; HADS, hospital anxiety and depression scale; HAQ, health anxiety questionnaire; EPQ-BV, Eysenck personality questionnaire—brief version; IES-R, impact of event scale revised; MI, myocardial infarction. *All data mean (range).
Our most striking finding was that both earthquakes differed in their effects on the pattern of acute cardiac admissions (Figure 6). In the two weeks following the September earthquake, there was an increase in acute ST-segment myocardial infarction (STEMI) presentations and a smaller increase in stress cardiomyopathy (Figure 7). Following the second earthquake, there were 3 times as many stress cardiomyopathy cases within 4 days, without a spike in acute myocardial infarction (Figure 8). The pattern following the first earthquake is similar to that reported after the 1994 Northridge earthquake. There was a 35% rise in myocardial infarction presentations in the week following Northridge. A similar sharp increase in the rate of myocardial infarction was reported in the week following the Kobe earthquake of 1995. In contrast, no increase in myocardial infarction rate was reported following the San Francisco earthquake. San Francisco occurred at 5:04 PM. Christchurch’s second earthquake, which also did not result in an increase in myocardial infarction, occurred at 12:51 PM. It is well known that circadian variation exists for myocardial infarction and sudden cardiac death. The risk of an acute cardiac event increases during the morning after waking and arising. Our data and the data from these other studies suggest that natural disasters occurring late in the morning and in the afternoon are much less likely to precipitate myocardial infarction than those occurring in the early hours of the morning. The 4 earthquakes with documented increases in acute myocardial infarction rates are the first Christchurch earthquake at 4:36 AM, Northridge at 4:30 AM, Kobe at 5:46 AM, and Newcastle at 10:27 AM.

Our data also raises the possibility of a circadian variation in the propensity toward stress cardiomyopathy. The earthquake at 12:51 PM in February...

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**Figure 6.** Total acute cardiology admissions. The increase in total cardiology admissions in the 2 weeks following the first earthquake was significant ($P=0.003$). Abbreviations: EQ, earthquake; wk, week.

**Figure 7.** Weekly STEMI Admission Rates Before and after the September Earthquake. Abbreviations: EQ, earthquake; STEMI, ST-segment myocardial infarction; wk, week.

**Figure 8.** Nonischemic cardiology admission rates. Abbreviations: CHF, congestive heart failure; EQ, earthquake; PE, pulmonary embolus; SCM, stress cardiomyopathy; VHD, valvular heart disease.
2011 was smaller than that at 4:36 AM in September 2010, but resulted in 3 times more cases. One other report of an earthquake stress cardiomyopathy cluster comes from the Niigata earthquake of 2004.11 That earthquake occurred at 13:01 PM. Watanabe et al reported 25 cases of stress cardiomyopathy in the 4 weeks after the event compared with only 1 case reported in the 4 weeks previously and none in the 2 years before.11

**A CASE OF RECURRENCE WITH A DIFFERENT PATTERN**

One of our most interesting cases of stress cardiomyopathy was a woman who presented after each earthquake with stress cardiomyopathy, with a different pattern on each occasion. She is not the first patient that we have seen with a different echo pattern on presentation, but we reported her given the identical nature of the stressor.

This 76-year-old woman first presented on September 4th after ten hours of chest pain. The electrocardiogram (ECG) showed inferolateral deep T wave inversion and QT prolongation.12 The levels of troponin I (TnI) peaked at 0.81 µg/L. Coronary angiography demonstrated diffuse atheroma with a moderate midleft anterior descending artery lesion that was stented at the time. ECG showed a classic takotsubo pattern. Her follow-up ECG on September 28th was normal and she was completely well at that point.

However, during the second earthquake on February 22, she again developed chest pain and shortness of breath. TnI levels peaked at 1.3 µg/L, and the ECG showed a midwall variant takotsubo with apical sparing. She was discharged from the hospital on February 29th, and was planning to leave Christchurch for a new home in another city, but returned for a follow-up ECG on July 27, which was normal.

The literature suggests that the recurrence rate of stress cardiomyopathy is low. In a case series of apical ballooning syndrome from the Mayo Clinic, the average yearly recurrence rate over the first few years was 2.9%.13 A systematic literature review found a similarly low recurrence rate of 3.5%.14 Recurrence with a differing pattern of left ventricular dysfunction is documented in a case report of a Japanese male with an intercurrent physical illness.15 A recent case report of a woman with a midventricular variant recurrence three years after an initial presentation with typical Takotsubo cardiomyopathy argues that genetic or other differences between patients cannot be responsible for the observed variable patterns of left ventricular dysfunction.16 Our report reinforces this and it also demonstrates that recurrence with a different pattern of left ventricular dysfunction can occur early with the repeat of the same stressor.

**ONE-YEAR FOLLOW-UP OF THE EARTHQUAKE CLUSTER**

So what happened to all of these women with stress cardiomyopathy? The 21 women who presented to Christchurch Hospital with stress cardiomyopathy within four days of the February earthquake represent a unique cohort.17 We systematically conducted a follow-up on these women at 12 months to ascertain what had happened to them—physically, psychologically, and socially.

Methods included a systematic review of the clinical files, electronic discharge summaries, imaging, and a telephone interview. A single investigator conducted the interviews in March 2012. A structured questionnaire was used to assess the patients’ self-reported cardiac and general health status. Patients answered questions about their cardiac symptoms, especially in relation to major aftershocks, hospital admissions, other noncardiac medical conditions, and treatment. After the initial telephone interview, psychometric questionnaires were also sent to the patients for consenting patients to complete.

All 21 stress cardiomyopathy patients were postmenopausal females with a median age of 68 years (52 to 85 years). Two patients presented with recurrent stress cardiomyopathy. One patient described above had presented after the first earthquake. Another woman also had a history of stress cardiomyopathy who had previously presented in August 2009 with apical ballooning triggered by an emotional stressor.

The average length of hospital admission was 37 hours (interquartile range, 7 to 51 hours). Two patients developed mild left ventricular failure and were successfully managed with oral frusemide treatment. No patient required inotropic support or intra-aortic balloon pump insertion. There were no deaths in this stress cardiomyopathy group during the study period.

At 12 months, all 21 stress cardiomyopathy patients were successfully interviewed. Two patients left Christchurch shortly after the 2011 earthquake. One had taken permanent residence in the North Island and the other had returned to live in Christchurch 13 months after the event. The remaining 19 patients stayed in Christchurch. Initially, six women still had chest pain after discharge. Five patients reported that they have experienced a few episodes of chest pain with aftershocks. All reported their symptoms settled by May 2012. There was no recurrence of stress cardiomyopathy in the 12-month follow-up period.

There were six hospital readmissions—five patients were admitted to the hospital and one patient had two admissions in the follow-up period. There were three cardiac-related admissions.
in March 2011. One patient re-presented one day after discharge with heart failure symptoms. She stayed in the hospital for another 24 hours and received treatment for heart failure. One patient presented nine days after she was discharged with chest pain. She was conservatively managed because she did not have new ECG changes or a significant rise in troponin levels. Another patient presented 28 days after initial discharge with atrial fibrillation requiring rate control treatment. There were three noncardiac related admissions that occurred later, which included exacerbation of chronic airway disease, pain due to compression fractures, and renal colic.

Most patients were treated with aspirin and β-blockade during and after admission with 43% receiving angiotensin-converting enzyme inhibitors (ACE inhibitors) or angiotensin receptor blockers (ARB). At follow-up appointments, most patients had the β-blockers discontinued. Our 12-month follow-up interview found that β-blockers and ACE inhibitors/ARBs were restarted in a number of cases; the patients reported that hypertension was the most common reason.

Seventeen patients completed the health assessment questionnaire (HAQ). Overall, nine patients had normal health anxiety levels (score 0 to 8), eight patients had a medium level of health anxiety (score 9 to 13), and no patient had a high level of health anxiety according to the test. Eighteen patients completed the hospital anxiety and depression scale (HADS). The test indicated that only five patients had borderline anxiety (score 9 to 13) and one had borderline depression (score 10).

The rest of the group did not have an abnormal level of anxiety or depression. Sixteen patients completed the impact of event scale revised (IES-R) questionnaires. Twelve patients were thought not to have posttraumatic stress disorder (PTSD) as they had normal scores (score 2 to 26), four patients might have had borderline PTSD as they had a score greater than 33 (score 39 to 45).

Our data shows that the patients could do well with a very short hospital admission. The cardiology staff had previous experience managing a cluster of stress cardiomyopathy patients following the September 2010 earthquake. This led to a high index of suspicion, therefore, rapid investigation and treatment. In the days following the earthquake, the hospital was under significant strain and there was pressure to discharge patients as soon as they were safe to leave. Patients who were stratified by their clinicians to be low risk had very short hospital stays—as short as three hours.

The Christchurch earthquake stress cardiomyopathy cohort had good short-term and medium-term outcomes without significant cardiac or psychological sequelae. Most patients remained healthy both physically and psychologically despite being exposed to incessant aftershocks following the February 2011 earthquake.

**FINAL THOUGHTS**

It is worth noting that only the two major earthquakes triggered stress cardiomyopathy despite the many aftershocks Christchurch endured. In fact, the vast majority of the 400 000 people exposed to this stressor did not develop stress cardiomyopathy. We would hypothesize that triggering of stress cardiomyopathy requires a “perfect storm” of genetic and environmental factors. These include, female gender, postmenopausal status, unknown or unrecognized genetic factors, sudden severe and unforeseen personal emotional stress, and perhaps an afternoon occurrence of that triggering event.

Earthquakes are common in New Zealand. We all grew up with periodic small shakes. Before 2010, none of us would have bothered putting our beer down and getting off the couch to take cover for an earthquake. What has occurred is out of the ordinary for us and was a powerful trigger for broken heart syndrome.

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Apical ballooning syndrome (Takotsubo cardiomyopathy) presenting with typical left ventricular morphology at initial presentation and mid-ventricular variant during a recurrence.
Takotsubo Cardiomyopathy

Summaries of Ten Seminal Papers

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Dialogues Cardiovasc Med. 2014;19:129-139

1. Transient left ventricular apical ballooning without coronary artery stenosis: a novel heart syndrome mimicking acute myocardial infarction
   K. Tsuei,
   and others. Am J Cardiol. 2001

2. Apical ballooning of the left ventricle: first series in white patients
   W. J. Desmet and others. Heart. 2003

3. Assessment of clinical features in transient left ventricular apical ballooning
   Y. Abe and others. Am J Cardiol. 2003

4. Neurohumoral features of myocardial stunning due to sudden emotional stress

5. Apical ballooning syndrome or takotsubo cardiomyopathy: a systematic review
   M. Gianni and others. Eur Heart J. 2006

6. Stress (Takotsubo) cardiomyopathy—a novel pathophysiological hypothesis to explain catecholamine-induced acute myocardial stunning
   A. Prasad and others. Am Heart J. 2008

7. Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction
   A. Prasad and others. Am Heart J. 2008

8. Clinical characteristics and cardiovascular magnetic resonance findings in stress (takotsubo) cardiomyopathy
   I. Eitel and others. JAMA. 2011

9. High levels of circulating epinephrine trigger apical cardiodepression in a beta2-adrenergic receptor/Gi-dependent manner: a new model of Takotsubo cardiomyopathy

10. A signature of circulating microRNAs differentiates takotsubo cardiomyopathy from acute myocardial infarction
    M. Jaguszewski and others. Eur Heart J. 2013

Selection of seminal papers by Gemma A. Figtree, MBBS, DPhil, FRACP, FAHA - North Shore Heart Research Group - Level 12 Kolling Institute (University of Sydney) Royal North Shore Hospital NSW 2065 - Australia

Highlights of the years by Sherri Smith, PhD
Publications division
Even though early reports had been published in the Japanese literature, it took the publication of a multicenter study reporting 88 cases of Takotsubo cardiomyopathy, in an international journal, to make a global impact. Members of the Angina Pectoris-Myocardial Infarction (AP-MI) used a Japanese national registry of patients to retrospectively analyze patients. Early reports described the features of Takotsubo cardiomyopathy, which include (i) acute, but transient, left ventricular apical wall motion abnormalities with chest pain; (ii) electrocardiographic (ECG) changes (eg, ST elevation or depression, abnormal Q wave), and (iii) minimal enzymatic release mimicking acute myocardial infarction (AMI) in the absence of angiographic stenosis. However, this was the first study to describe clinical characteristics associated with the syndrome in a more general sense. This allowed the features that are now considered “classic,” such as female preponderance (6.3-fold higher than in men) and postmenopausal status of most patients, to be associated with Takotsubo cardiomyopathy.

Although encouraged to use the terminology “apical ballooning” in the title, the authors provide a historical context for this terminology by referencing an earlier work by Satoh et al where the “Takotsubo” nomenclature was used and explained the similarity to the Japanese octopus pot. The authors also noted the important similarity between Takotsubo cardiomyopathy and apical wall motion abnormalities observed in association with intracranial events and pheochromocytoma as well as other systemic conditions.

In addition to the postmenopausal female preponderance, important clinical features that are described in this large cohort include: (i) ECG morphology variability of patients presenting with the condition, (ii) the relatively low rise of cardiac enzymes; and (iii) the variety of triggers (eg, emotional, physical, procedural, periprocedural). Although the tendency for rapid recovery is noted, potential dangers are associated with the condition including the incidence of ventricular arrhythmias (9%), the requirement for balloon pump support (8%), and the mortality rate (1%). The 19% rate of inotropic support (dopamine/dobutamine) is of particular relevance in the context of a recently proposed hypothesis by Lyon, which highlights the pathophysiological reasons why catecholaminergic inotropes may, in fact, be harmful.

The authors also discussed the common development of intraventricular pressure gradients, which were observed in 18% of the total cohort. In one example, the patient reached a pressure as high as 75 mm Hg.

The prior predominant hypothesis was that this syndrome was secondary to a generalized multivessel spasm. Perhaps one of the most important contributions of this study regarding the prior predominant hypothesis is the finding that only 10 out of 48 patients with intracoronary acetylcholine had a provoked vasospasm. Although this observation did not exclude a role for microvascular dysfunction, it did open up the possibility for other Takotsubo cardiomyopathy mechanisms.

Sherpa Temba Tsheri, 16, becomes the youngest person to summit Mount Everest; the world’s first self-contained artificial heart is implanted in Robert Tools; and Marie José of Belgium (Marie José Charlotte Sophie Amélie Henriette Gabrielle), the last Queen of Italy, dies at age 94 of lung cancer.
Apical ballooning of the left ventricle: first series in white patients

W. J. Desmet, B. F. Adriaenssens, J. A. Dens

*Heart.* 2003;89:1027-1031

Following the publication of a large Japanese cohort of patients with takotsubo cardiomyopathy by Tsuchihashi et al (reviewed in the previous seminal paper summary), doubt remained as to the relevance of the condition to the rest of the world beyond Japan. Desmet et al described 13 white patients with Takotsubo cardiomyopathy by evaluating many parameters including: sex, age, presenting symptoms, duration of symptoms before admission, serial ECGs, QT interval, cardiac enzymes, cardiac imaging, invasive pressures, cardiac index, wedge pressure, the use of intra-aortic balloon counterpulsation, pathological finding, and parameters of recuperation.

This study by Desmet et al was the first to highlight the amazing reproducibility of the constellation of clinical features that includes: (i) an acute onset of transient extensive akinesia of the apical and midportion of the left ventricle; and (ii) no significant stenosis on the coronary angiogram. These features are accompanied by chest symptoms, ECG changes, and a limited release of cardiac markers disproportionate to the extent of akinesia. In surviving patients, the left ventricle function completely recovered within a few weeks. Desmet et al also demonstrated an apparent lack of racial influence and was the first to establish that this syndrome also occurs in a white population. The age range, high proportion of female Takotsubo patients, and the severity of presentation were all very similar to the published Japanese results.

The timing of this syndrome’s recognition worldwide appears to be related to rapid triage and improvement in imaging techniques. The early identification of the syndrome by the Japanese clinicians was more likely related to the practice of rapid triage for angiography and early imaging of coronary anatomy and ventricular function rather than a unique Japanese predisposition. In addition, the national registry for patients with myocardial infarction allowed the Japanese to identify the unifying features of this condition. Investigators of Takotsubo cardiomyopathy are driven not only by curiosity about the syndrome, but also by the underlying pathophysiology, which likely has important implications to a broader range of cardiac conditions. The lengthy discussion of possible pathophysiological mechanisms by Desmet et al, which is a general feature of the many manuscripts published in the ensuing years, is worthy of comment, particularly given the paucity of evidence that had been available.

The age of the universe is accurately determined—with just a 1% margin of error—to be 13.7 billion years old; the planet Mars makes its closest approach to Earth in over 50,000 years during a perihelic opposition; and a blackout cuts power to an estimated 10 million people in Ontario, Canada and 45 million people in eight states in the USA.
Assessment of clinical features in transient left ventricular apical ballooning

Y. Abe, M. Kondo, R. Matsuoka, M. Araki, K. Dohyama, H. Tanio

*J Am Coll Cardiol.* 2003;41:737-742

Be et al performed a small, but important, mechanistic study on a series of 17 consecutive patients between April 1, 1996 and March 31, 2001 who met the following criteria: (i) reversible balloon-like left ventricular wall motion abnormality at the apex with hypercontraction of the basal segment; (ii) ST-T segment elevation or T-wave inversion in several leads on the electrocardiogram; (iii) no history of a previous myocardial infarction; and (iv) no complication with a subarachnoid hemorrhage or a pheochromocytoma crisis. The study conducted coronary physiological studies and utilized Doppler guidewire to evaluate the diastolic to systolic velocity ratio, the deceleration time of the diastolic flow velocity, the early systolic reverse flow, and the coronary flow reserve. In addition, quantitative technetium-99m tetrofosmin (TF)-gated single-photon emission computed tomographic myocardial imaging was conducted for both the acute and chronic phases. A multiple-plane coronary angiogram was performed on 7 patients during the acute phase, 5 during the chronic phase, and 4 during both acute and chronic phases. 6 patients also underwent myocardial biopsy to determine, for the first time, the underlying pathology.

Scintigraphy demonstrated an 85% reduction in TF uptake at the apex, which was considered independent of any macro- or micro-vascular perfusion abnormality. This was suggestive of a metabolic abnormality, and the authors discussed the possibility of this abnormality being secondary to a toxic effect of locally released noradrenaline. This theme has been pursued over the following decade in the field. Abe et al demonstrated that: (i) ST-T segment and wall motion abnormalities were transient and reversible; (ii) the involvement of epicardial coronary artery stenosis, vasospasm, and disturbance of microcirculation was minimal; (iii) physical or emotional stress served as triggers in approximately 94% of patients; and (iv) pathologic evidence of acute myocarditis was minimal.

The elegant microvascular studies performed in this small study also made a significant impact on future studies. Although the theory of epicardial coronary artery spasm had been previously refuted, this study demonstrated, for the first time, that a deleterious effect on the coronary microcirculation was not a major mechanism involved in the pathophysiology of the syndrome.

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**2003**

An earthquake in the Boumerdès region of northern Algeria kills 2200;

Paul Bahn, Sergio Rippoll, and Paul Pittit discover engravings and bas-reliefs on the walls and ceilings of some of the caves at Creswell Crags, an important find as it had previously been thought that no British cave art existed; and

Pope John Paul II, the first non-Italian pope elected in more than four hundred years, celebrates his silver jubilee in Rome
Neurohumoral features of myocardial stunning due to sudden emotional stress


With this manuscript by a team at John’s Hopkins Hospital, Takotsubo cardiomyopathy had reached “prime-time” in the international literature. Although extensive multimodality characterization was performed, the most novel aspect of this work was the study of neurohumoral levels in a patient cohort that was homogenous because they all had an emotional precipitant. The neurohumoral levels were measured at multiple time-points, and expert attention was paid to the preparation of samples, including ensuring that the patients remained supine for at least 60 minutes prior to phlebotomy.

The choice of a control group was always going to provide problems for investigators, and it is surprising that multiple control groups were not included, and that the control group chosen was very small. The authors performed parallel studies in only 7 female patients with myocardial infarction, who were chosen in an attempt to be a match for the sympathetic tone driven from the myocardial dysfunction itself.

Additional issues, which somehow did not stop this manuscript from being accepted by a premier medical journal, include: (i) the sporadic nature of the phenotyping (eg, only 5 women (26%) had a biopsy and only 5 women (26%) underwent cardiac magnetic resonance imaging); and (ii) one of the women included in the Takotsubo cohort had a 70% obstructive LAD stenosis. The acceptance of the manuscript for publication in the New England Journal of Medicine perhaps reflects the “early days” nature of the Takotsubo syndrome being recognized by the field and its international intrigue.

The strengths of the study revolve around the key findings that patients with emotional stress-induced cardiomyopathy had supraphysiological levels of plasma catecholamines and stress-related neuropeptides, with evidence of prolonged activation of the adrenomedullary hormonal system beyond one week after the onset of symptoms. These findings greatly strengthened the fields’ focus on abnormalities in catecholamine signaling as a primary player in the pathophysiology of Takotsubo cardiomyopathy. Furthermore, because their data implicated massive catecholamine release, the authors discussed their avoidance of pressors and β-agonists where possible, suggesting alternative mechanical circulatory support in patients that are severely and hemodynamically compromised.

Although some of the strengths of this study have been highlighted above, the finding of elevated circulating catecholamines, or indeed, the histological feature of catecholamine toxicity, with contraction band necrosis, has been controversial and has not been a consistent observation in all ensuing studies.

Rosa Parks, an American civil rights activist, dies at age 92; Eris, the largest known dwarf planet in the Solar System, is identified by a team led by Michael Brown using images originally taken on October 21, 2003, at the Palomar Observatory; and Kuwaiti women are granted the right to vote
Gianni et al performed a systematic review of the literature to clarify the prevalence, clinical characteristics, natural history, prognosis, and pathophysiology of the transient left ventricular (LV) apical ballooning syndrome, which is also called Takotsubo cardiomyopathy. Given the relatively small number of patients in an increasing number of published reports on Takotsubo cardiomyopathy, this well-conducted systematic review published in 2006, has been helpful to investigators and clinicians in the field. Gianni et al performed an admirable job given the difficult job of assessing the predominantly small studies, enabling them to conduct a combined analysis on 286 patients.

In stating their inclusion criteria for the review, the authors effectively began to solidify the diagnostic criteria for Takotsubo cardiomyopathy, which had not been formalized prior to this review. Inclusion criteria involved: (i) publications that reported original data; (ii) studies with at least 5 patients; (iii) patients with transient akinesis or dyskinesia of the LV apex and wall motion abnormalities involving the midventricular LV segment that were not restricted to a single coronary artery territory; (iv) patients who had undergone coronary angiography revealing no obstructive coronary artery disease (defined as >50%) and no acute plaque rupture; and (v) at least one of the following: prevalence, clinical presentation, natural history, long-term prognosis, and underlying pathophysiological mechanisms of the apical ballooning syndrome.

The authors reported that the prevalence of the apical ballooning syndrome was still uncertain and clearly demonstrated that there is a marked gender discrepancy, with the disease being more common in women (≈88.8%). The most common clinical symptoms at presentation were chest pain and dyspnea, and the most serious clinical presentations included cardiogenic shock and ventricular fibrillation. The most common electrocardiographic abnormalities included ST-segment elevation and T wave inversion, which is usually observed during the acute and subacute phases. During the acute phase, all patients had moderate to severe midventricular dysfunction and apical akinesia or dyskinesia. Midventricular and apical wall motion abnormalities completely resolved in all surviving patients.

This review provided a baseline to guide clinicians and make them aware of the existence and the typical clinical manifestations of this syndrome. Future studies are required because many questions remain regarding the etiology, pathophysiology, and management of this syndrome.

Grigori Perelman declines the prestigious Fields Medal after solving the complex mathematical problem known as Poincare’s Conjecture, which originated in 1904; Edgar Valter, an Estonian writer and illustrator of over 250 children’s books, dies at age 76; and Ireland claims the Triple Crown in rugby for the second time in 3 years.
his review and proposal of a novel mechanism for Takotsubo cardiomyopathy is by one of the world-leading laboratories in the field of β-adrenergic signaling in the myocardium. Although the manuscript contains no novel data, the evidence laid out to support a novel hypothesis is strong and has had a substantial impact on the field’s search for pathophysiological explanations of the phenomenon.

The authors build on the observed relationship of Takotsubo syndrome with emotional and other forms of stress, and the finding of persisting high catecholamine levels. The laboratory, with a prior impressive record in characterizing the direct effects of adrenaline (epinephrine) on the ventricular myocardium, proposes that the Takotsubo syndrome represents a form of epinephrine-mediated acute myocardial stunning. They refer to the known differential distribution of cardiac β2-adrenoreceptors (β2ARs), being higher towards the apex in association with lower sympathetic nerve density. β2ARs are known to switch from Gs protein signaling to Gi protein signaling after exposure to high adrenaline, which results in negative inotropic responses to the persistently elevated catecholamines, therefore the β2AR gradient provides a credible explanation for the apical predilection of the akinesis.

Importantly, the hypothesis and prior cell-based findings that the authors refer to, provide a mechanism for the myocardial dysfunction and the observed rapid recovery. Their hypothesis stated that after the surge of adrenaline has passed, the β2ARs that had undergone “stimulus trafficking,” and are actively mediating negative inotropy, either switch back to Gs protein-coupling, or become internalized, and degraded.

The authors of this manuscript push forward an argument, similar to Wittstein et al, that it appears illogical to treat patients with stress cardiomyopathy and cardiogenic shock with inotropic agents, particularly dobutamine. Although these recommendations remain to be tested in an appropriately designed clinical trial, the recommendations for preferential use of levosimendan over the catecholamine-based approach has been adopted by clinicians around the world who are aware of this hypothesis, as well as the animal data published by the Harding laboratory in 2012, which is discussed in the seminal paper summary 9 (page 138).

Stress (Takotsubo) cardiomyopathy—a novel pathophysiological hypothesis to explain catecholamine-induced acute myocardial stunning

A. R. Lyon, P. S. Rees, S. Prasad, P. A. Poole-Wilson, S. E. Harding


The longest serving ocean liner in history, the Queen Elizabeth 2 (QE2), is retired from service; an extra leap second (23:59:60) is added to the end of the year; and Charlton Heston, an American actor who won the Academy Award for best actor for his role in the movie Ben Hur, dies at age 84
Investigators from the Mayo Clinic have made steady and important contributions to the characterization and understanding of Takotsubo cardiomyopathy since its recognition. This manuscript by members of the team at the Mayo Clinic not only provides an excellent review of the prior literature, but also highlights the need for more evolved diagnostic criteria. The criteria they proposed, which builds on previously tabled criteria published in 2004, takes into account the anatomical variant of apical sparing, and allow for patients with nonobstructive coronary disease to be diagnosed with Takotsubo cardiomyopathy. The criteria are listed as:

1) Transient hypokinesis, akinesis, or dyskinesis of the left ventricular midsegments with or without apical involvement; regional wall motion abnormalities that extend beyond a single epicardial vascular distribution; a stressful trigger is often, but not always, present.
2) Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture.
3) New electrocardiographic abnormalities (ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin.
4) Absence of pheochromocytoma or myocarditis.

An important discussion point covered in this manuscript is the significant variability in the frequency of ST elevation reported in the literature, ranging between 46% and 100%. They astutely identified contributing factors to this reported variability, including the transient nature of ST elevation, as well as selection bias for patients presenting with ST segment elevation to be triaged promptly for angiography, thus capturing the classical abnormality of left ventricular systolic function prior to its rapid recovery.

The authors also devoted considerable time in this manuscript to provide advice to readers about their theories on the optimal management of Takotsubo cardiomyopathy patients. They provided a practical approach, highlighting the lack of evidence for any specific therapy, but the general success of supportive measures. Despite acknowledging the potential pathophysiological role of catecholamines, the authors were still advising readers that “cardiogenic shock” should be treated with “inotropes” in addition to intra-aortic balloon counterpulsation. The tendency to advise intensive care physicians against catecholamine-based therapies has increased after the publication of the Lyon hypothesis, and animal models supporting the likely advantage of levosimendan as an alternative. In many countries, despite the logic behind this, the higher financial cost of levosimendan, rules against the common acceptance of this practice.

I

Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction

A. Prasad, A. Lerman, C. S. Rihal

Am Heart J. 2008;155:408-417

Ashrina Furman runs a mile on spring-loaded stilts in 7 min 13 sec setting a new world record; a human stampede at a Hindu temple at Naina Devi in Bilaspur, Himachal Pradesh, India, kills 162 and injures 400; and Claudia Castillo of Spain becomes the first person to have a successful trachea transplant using a tissue-engineered organ
Clinical characteristics and cardiovascular magnetic resonance findings in stress (takotsubo) cardiomyopathy


JAMA. 2011;306:277-286

This multicenter study is extraordinary in regard to both the large numbers of patients with stress cardiomyopathy that have been recruited (n=256), and the detailed cardiac magnetic resonance imaging performed at the time of presentation, as well as 1 month and 6 months into recovery. The investigators include international experts in the cardiac magnetic resonance (CMR) field, with particular knowledge of the application of CMR to imaging interstitial edema and fibrosis.

CMR was used to characterize the functional and myocardial features of Takotsubo cardiomyopathy in a manner that was not possible with either echocardiography or ventriculography. For the first time, investigators were able to precisely quantify right ventricular (RV) function in a large cohort of patients, finding that 34% of the cohort had RV “ballooning.” The large size of the cohort allowed investigators to demonstrate that this was associated with severity of left ventricular dysfunction, as well as a higher frequency of preceding stressful events, and that impaired RV function was a risk factor for longer hospital stays.

Coming from international leaders in CMR-imaging of the myocardial, including Matthias Friedrich, this study was meticulous in its acquisition of T2-weighted images and early postgadolinium datasets designed to sensitively and specifically detect myocardial inflammation. Using this approach, the investigators demonstrated that 81% of patients had myocardial inflammation, which was transmural and matched the distribution of LV dysfunction. (ie, mid-ventricular to apical). The authors observed that the transmural distribution of the edema is distinct from the classic patterns of myocarditis that is predominantly subepicardial and most often inferolateral, which likely has diagnostic relevance.

In contrast to the T2-weighted edema imaging, foci of patchy late-gadolinium enhancement were infrequently observed, in only 9% of the total cohort, and only in those with the most severe presentations and highest troponin elevations. Furthermore, the demonstration of any late gadolinium enhancement was only with a considerably reduced threshold compared with the analysis of patients with myocardial infarction, using a signal intensity–difference threshold of 3 standard deviations (SD). When the investigators applied the more commonly used SI threshold of 5 SD, no patient was found to have evidence of late-gadolinium enhancement.

The exquisite CMR characterization of this large, multicenter cohort study provides some hope that we will be able to distinguish and triage individuals with Takotsubo cardiomyopathy, in order to avoid the need for invasive angiography. Such a possibility is most likely, initially, for patients without ST elevation. In this cohort of patients, who do not have an urgent indication to be transferred to the catheter laboratory, it is already feasible that a combination of detailed CMR following the protocol laid out in this manuscript, perhaps with CT coronary angiography, would assist in confirming the diagnosis of Takotsubo cardiomyopathy and avoiding the catheter laboratory.

Iceland’s most active volcano, Grímsvötn, erupts making it the largest eruption in Iceland for 50 years; a pill to prevent sunburns is being developed using coral’s natural defense against the sun’s harmful ultraviolet rays; and Ronald Searle, a British artist and satirical cartoonist, dies at age 91
High levels of circulating epinephrine trigger apical cardiodepression in a beta2-adrenergic receptor/Gi-dependent manner: a new model of Takotsubo cardiomyopathy


*Circulation.* 2012;126:697-706

Paur et al provide the Takotsubo field with novel mechanistic and therapeutic insights using a novel animal model of Takotsubo syndrome. The experimental data also has relevance to understand beta-adrenergic signaling in cardiac pathophysiology in a broader sense. This study is a fantastic example of the value of “bed-to-bench-side” research. The experimental design and manuscript builds from the “Lyon” hypothesis, previously published by this group in *Nature Clinical Practice Cardiovascular Medicine* in 2008, and discussed in the seminal paper summary number 6 (page 135). The investigators, therefore, examined whether Takotsubo cardiomyopathy results from a switch of adrenaline signaling through the beta2-adrenergic receptor (beta2AR) from a stimulatory G-protein-activated cardiostimulant to an inhibitory G-protein-activated cardiodepressant pathway.

In this study, rats received high-dose, intravenous bolus injections of adrenaline or noradrenaline, with or without specific pharmacological inhibitors, and then underwent detailed monitoring of cardiovascular parameters, including serial echocardiography. Patients with Takotsubo cardiomyopathy typically have a prominently elevated adrenaline vs noradrenaline. Therefore, the adrenaline administration successfully induced a Takotsubo-like phenomenon, with impaired left ventricular (LV) contractility being the highest at the apex and midventricular segments. Rapid recovery was also mimicked in this model, with normal LV contractility achieved at 1-hour postadrenaline bolus. Having reproduced the Takotsubo phenotype with high-dose adrenaline, investigators confirmed the role of Gi signaling, by abolishing it with pertussis toxin pretreatment (*in vivo*).

Parallel studies were also performed on primary cultured rat cardiac myocytes, examining the effect of beta2AR overexpression. The reproduction of the negative inotropic response to adrenaline, with a switch from Gs to Gi, in isolated myocytes further supports the predominant role of cardiomyocyte dysfunction in Takotsubo cardiomyopathy rather than the previously postulated vascular dysfunction. The investigators also addressed the clinically important issue of the most appropriate therapeutic approach to counter the negative inotropy mediated by the switch of beta2AR to Gi signaling: intravenous propranolol, carvedilol, or levosimendan infusions were administered 15 minutes after epinephrine injection. In contrast to either propranolol or carvedilol, levosimendan administration showed strong therapeutic potential, preventing further decline in cardiac function. The clinical relevance of this time point, however, given patients suffering from Takotsubo cardiomyopathy do not present until the clinical syndrome secondary to the negative inotropy occurs, is uncertain. The additional observation that a high-dose noradrenaline bolus does not reproduce the takotsubo phenotype, and the molecular switch from Gs to Gi signaling via the beta2AR, suggests that physicians might be able to use noradrenaline for pressor support in a relatively safe manner.

The Lyon/Harding team had previously postulated that the beta2AR switch to Gi was an essential protective mechanism employed by the myocardium in conditions of sudden adrenaline surges. The demonstration, in this study, of the dramatic increase in acute mortality rates in rats receiving adrenaline when preloaded with a selective beta2AR pharmacological antagonist certainly support this, and is an example of the broader relevance of this manuscript to the heart failure field in general.

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Betty White, an American actress, wins a Grammy Award at age 91 making her the oldest person to receive this award; Austrian skydiver Felix Baumgartner becomes the first person to break the sound barrier without mechanical assistance; and The Shard, the tallest building in the European Union and the tallest habitable freestanding structure in the UK, is officially opened.
A signature of circulating microRNAs differentiates takotsubo cardiomyopathy from acute myocardial infarction


Jaguszewski et al provide us with the first published data on the potential for circulating microRNAs (miRNAs) to be diagnostic biomarkers for Takotsubo cardiomyopathy. This is important in the context of the paucity of diagnostic tools available for clinicians in the acute setting to differentiate between Takotsubo cardiomyopathy and acute coronary artery occlusion with associated myocardial infarction. The manuscript is based on the increasing appreciation of the role of this class of highly conserved, noncoding nucleotides in cell proliferation, angiogenesis, differentiation, and apoptosis in cardiovascular physiology and pathophysiology.

The investigators recruited 36 patients from 5 contributing centers to the International Takotsubo Registry (www.takotsubo-registry.com). Plasma samples were taken within 24 hours of presentation. Although this study is thought provoking, a major limitation of the study is the very few number of patients, particularly when the investigators use arrays that contained probes for a total of 667 human miRNAs for their first pass investigations. Although each of the “hits” from this pooled screening round were then quantified using quantitative RT-PCR in individual patients in the validation step, it does not completely take away from the “fishing expedition” nature of this study.

Interestingly, of the 36 patients diagnosed with Takotsubo cardiomyopathy, 3 were included despite having obstructive coronary artery disease (with at least one stenosis >50%). This highlights the potential usefulness of the Mayo criteria #1, which emphasizes that the wall motion abnormality must extend beyond a single coronary territory. However, it is not completely without controversy, given that it disregards the Mayo criteria #2, requiring an “absence of obstructive coronary disease or angiographic evidence of acute plaque rupture.”

The main findings of the study reported are the upregulation of miR-16 and miR-26a in patients with Takotsubo cardiomyopathy compared with healthy subjects, and the upregulation of miR-16, miR-26a, and let-7f compared with STEMI patients. Obviously, these findings need validating in larger study populations. An interesting extension of this work for future studies would be to examine the change of microRNA in the recovery period, and in the time-period remote from the presentation, compared with appropriate controls. If the pattern of miR-16, miR-26a, and let-7f microRNA upregulation in Takotsubo cardiomyopathy patients compared with STEMI patients is confirmed in future studies, it may have clinical utility in the emergency room. However, for this to occur, the ability to detect this distinctive pattern must be reproduced in the early stages of patient presentation. The timing of plasma collection in this study was not rigorously defined and occurred sometime within 24 hours of presentation.

If the miRNA pattern in Takotsubo cardiomyopathy is validated, mechanistic hints may be elucidated. In this manuscript, the authors make the biologically plausible link between miRs-125a and 5p, which was downregulated in patients with Takotsubo cardiomyopathy, and its possible role in the pathophysiology via its known effect on endothelin-1 levels. Their findings that ET-1 levels were significantly increased in the Takotsubo cohort were supportive of this, however, causality remains to be tested.

Queen Beatrix of the Netherlands abdicates in favor of her son the Prince of Orange, who becomes the first male monarch in 123 years; doctors in Massachusetts, USA invent a pill-sized medical scanner that can be safely swallowed by patients, allowing the esophagus to be more easily scanned for diseases; and French president François Hollande receives a baby camel by the government of Mali for helping rid the north of Islamist rebels
## Bibliography of One Hundred Key Papers

**selected by Alexander R. Lyon, MA, BM, BCh, MRCP, PhD**

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Summer preference in the occurrence of takotsubo cardiomyopathy is independent of age.  

Monday preference in onset of takotsubo cardiomyopathy.  


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