Review Article

Takotsubo Cardiomyopathy: The “Broken Heart” Syndrome

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Takotsubo cardiomyopathy (TTC), a seemingly rare but in fact under-recognized transient left ventricular dysfunction, is a clinical entity mimicking an acute coronary syndrome. Its main characteristics are chest pain, ischemic electrocardiographic changes, mildly elevated cardiac enzymes and wall motion abnormalities. First reported in the Japanese population by Hikaru Sato et al at the beginning of the previous decade, TTC was given its name because, in the classic form of the disease, the left ventricle in systole has the shape of a “takotsubo”, a pot used by the Japanese to catch octopus, with a narrow neck and a wide round bottom (Figure 1). The syndrome was initially thought to affect almost exclusively the Japanese population for some unknown genetic or behavioral reasons. However, during the last decade several cases have been reported worldwide, indicating that it is extremely unlikely to be a geographically isolated disease. Moreover, several variants of TTC have been described that involved different segments of the ventricular wall. Multiple names have also been used (stress cardiomyopathy, “ampulla” cardiomyopathy, transient left ventricular apical ballooning syndrome, “broken heart syndrome”, neurogenic myocardial stunning). Indeed, in 2006, under the name “stress cardiomyopathy”, it was classified within the group of acquired cardiomyopathies. A major stressful event (emotional or physical) precedes the onset of symptoms, although not in every patient. Its course is usually benign and a full recovery is expected in the majority of cases.

Epidemiology

The prevalence of the disease is unknown. In Japan it is estimated to be as high as 1-2% of hospital admissions for chest pain and acute dynamic ST-segment electrocardiographic changes. In the United States 2-2.2% of the patients presenting with the clinical picture of an ST-segment elevation acute myocardial infarction (STEMI) or unstable angina are ultimately diagnosed with TTC. It seems, however, that these percentages underestimate the true prevalence of the disease, which in the thrombolysis era prior to the wide application of primary angioplasty must have gone unnoticed on several occasions. Notably, since TTC has become more widely recognized and more specific diagnostic criteria have been established, higher prevalence rates have been reported (for example, 4.78% in the recently published study of Facciorusso et al).

Moreover, studies in specific populations have shown a much higher incidence. Park et al reported that one third of the patients they studied, who were ad-
mitted to a medical intensive care unit with a non-cardiac diagnosis (respiratory failure or sepsis), suffered from transient left ventricular apical ballooning. An increased incidence of chronic obstructive pulmonary disease or bronchial asthma was found by Hertting et al.\(^9\) in 32 patients diagnosed retrospectively with TTC. In addition, the prevalence of hypertension in TTC patients has been reported to be as high as 76%.\(^10\) All these findings offer some evidence supporting the hypothesis that catecholamine surge may play an important role in the pathogenesis of the syndrome.

A strict predilection for female gender and for older age is one of the hallmarks of TTC, with postmenopausal women reported to make up over 90% of the cases in most series.\(^11-13\) Nevertheless, there are some exceptions to this rule, since a higher proportion of premenopausal women are affected by the apical-sparing variant of the disease,\(^14\) while a male predominance has been reported in the cases precipitated by physical stress.\(^15\) The reason for the female predominance remains essentially unknown, although a lack of estrogen in the postmenopausal phase seems to play a pathogenetic role. A stressful emotional or physical event seems to be the precipitant in about two thirds of the cases reported. Although the myocardial dysfunction typically follows an acute psychological trigger (unexpected loss of a close relative, confrontation with another person, devastating financial loss, fear prior to a medical procedure, etc.), a physical stress (pulmonary disease, sepsis, trauma, cerebrovascular accident) is equally likely to be the preceding event. Caucasians may be more susceptible to emotional stress in comparison to Asians.\(^16\)

**Pathogenesis**

The pathogenetic mechanisms underlying the development of this rare, transient cardiac dysfunction remain largely unknown. Several theories have been proposed. Catecholamine surge definitely plays a role, but the way it affects myocardial function has not been clarified. The presence of occult coronary atherosclerosis with plaque rupture leading to acute ischemia has been advocated, mainly by Ibanez et al.\(^17\)

All the patients reported by this particular group had a similar pattern of coronary artery anatomy, with a long left anterior descending (LAD) branch wrapped around the apex. This type of anatomy can explain the extensive apical akinesis of TTC. However, the development of even transient myocardial ischemia, especially in the setting of occult coronary artery disease, requires the additional presence of intracoronary thrombus, a feature that has never been demonstrated in TTC patients. Moreover, a long LAD artery has not been described by other authors. In another theory, coronary spasm has been thought to be the triggering event. Multivessel spasm has to occur in order to explain the wall-motion abnormalities extending beyond the territory of a single epicardial coronary vessel. Indeed, some have been able to provoke multivessel spasm in patients with TTC,\(^11,18\) although others have failed to do so.\(^19,20\)

In addition, the routine administration of nitrates in patients presenting with chest pain would obscure such a mechanism.

Microvascular dysfunction and spasm have also been thought to be the cause of TTC. Elesber et al.\(^21\) reported an abnormal TIMI myocardial perfusion grade (an angiographic index of myocardial perfusion) in 69% of their TTC patients. In addition, Sadamatsu et al.\(^22\) were also able to show diminished coronary flow reserve in their patients, using a Doppler guide wire. On the other hand, Yoshida et al.\(^23\) found only mild perfusion impairment with Thallium-201 single-photon emission computed tomography in their TTC patients. In contrast, severely reduced uptake was found at the apex of F-8 fluorodeoxyglucose positron emission tomography images, suggestive of a metabolic rather than a perfusion defect. Thus, it remains unknown whether microvascular dysfunction plays a causative role in TTC or whether, when observed, it is a consequence of a primary myocardial impairment process.

**Figure 1.** The Japanese octopus-catching (takotsubo) pot.
The hypothesis of acute myocarditis as the cause of this impairment has not been confirmed by the studies where endomyocardial biopsies were performed.\textsuperscript{24,25} Structural and ultrastructural myocardial changes are rather suggestive of direct catecholamine toxicity. Since the first report by Wittstein et al\textsuperscript{24} about increased catecholamine plasma levels in patients with TTC, another more recent study has confirmed those authors’ findings, reporting increased local release as assessed by blood sampling from the aortic root and the coronary sinus.\textsuperscript{26} In experimental animals, an increased density of \( \beta \)-adrenoreceptors in the cardiac apex has been observed.\textsuperscript{27} If this is also true for the human heart, it could potentially explain the increased susceptibility of the apex to the direct toxic effect of catecholamines. This hypothesis remains to be proven, however.

A more detailed model of explanation, involving a switch in intracellular signal trafficking in cardiomyocytes from \( G_s \) protein to \( G_i \) protein signaling via the \( \beta_2 \)-adrenoreceptors, leading to transient negative inotropism, has been proposed by Lyon et al.\textsuperscript{28} This intriguing hypothesis also awaits confirmation. The development of transient severe left ventricular outflow obstruction is another mechanism that has been implicated in the pathogenesis of TTC.\textsuperscript{29} In the setting of a massive catecholamine surge, elderly women, who frequently have a sigmoid septum, could potentially develop severe obstruction, leading to apical ischemia as a result of increased wall stress. Although a significant gradient has been reproduced with dobutamine infusion in some TTC patients, this mechanism cannot explain the apical sparing variants of the disease. Nevertheless, it could represent a contributing cause in some cases. Lastly, a neurally mediated mechanism has been proposed. A pattern of apical dysfunction similar to that of TTC has been observed in patients with subarachnoid hemorrhage. Interestingly, this has been associated with rupture of aneurysms located in the anterior half of the circle of Willis. These aneurysms overlie the amygdala and the right insular cortex, which control sympathetic outflow to the heart.\textsuperscript{30} Although this last hypothesis offers both an anatomic and a functional explanation of stress-induced myocardial dysfunction, there is not currently any strong clinical or experimental evidence to support it.

**Clinical characteristics**

The clinical picture of TTC is frequently indistinguishable from that of an acute coronary syndrome. Chest pain is an almost ubiquitous finding (100% in most of the series). It is sometimes accompanied by dyspnea, palpitations, diaphoresis, nausea or syncope. Less frequently, hemodynamic instability with hypotension or true cardiogenic shock, requiring circulatory and ventilation assistance, becomes a prominent characteristic of the clinical picture.\textsuperscript{24} Electrocardiographic (ECG) findings usually mimic those of an acute ST or non-ST elevation myocardial infarction (Figure 2). Sharkey et al\textsuperscript{31} studied thoroughly the electrocardiograms of 59 patients diagnosed with TTC. On admission, 56% of the patients had ST-segment elevation, while 17% presented with T-wave inversions and 10% with Q-waves or abnormal R-wave progression. Notably, the remaining 17% of the patients had either non-specific changes or no changes at all. During the recovery phase, new or deepening T-wave inversion (most prominently in leads V\textsubscript{2} to V\textsubscript{6}) was the most frequent electrocardiographic feature. In the same study, the average magnitude of the

![Figure 2. Acute ST-segment elevation in leads V\textsubscript{2}-V\textsubscript{6} (arrows) upon presentation (A) followed by T-wave inversion in the same leads (arrows) 2 days later (B) in a patient with takotsubo cardiomyopathy (our case).](image-url)
ST elevation was less in those with TTC in comparison to patients who had LAD coronary artery occlusions. However, the considerable overlap among individual values precludes any diagnostic significance for these ECG features. QTc interval lengthening and R-wave reappearance were the other most common evolutionary changes. Other authors have reported that TTC patients develop deeper T-wave inversions or more prolonged QTc intervals than CAD patients.\textsuperscript{32} The absence of reciprocal changes in the inferior leads and a ratio of ST-segment elevation in leads V\textsubscript{4}-V\textsubscript{6} to V\textsubscript{1}-V\textsubscript{3} ≥1 have also been considered highly specific for TTC.\textsuperscript{33} Even these findings, however, are too subtle to be helpful in the differential diagnosis between TTC and an acute coronary event in everyday clinical practice. The time course of these ECG changes in TTC seems similar to that observed in patients with early reperfused ST-elevation acute myocardial infarction, with T-wave inversion persisting for at least 2-3 weeks.\textsuperscript{32}

Minimally elevated cardiac markers suggestive of mild myocardial injury are frequently measured. On the other hand, cardiac imaging studies usually reveal extensive apical and/or mid-ventricular akinesis or hypokinesis with basal sparing, discordant with the minimally increased cardiac enzymes. These wall motion abnormalities typically extend beyond the vascular territory of a single coronary artery, suggesting that myocardial stunning rather than necrosis is the underlying mechanism of the acute left ventricular dysfunction. A small proportion of patients do not have elevated cardiac enzymes at all. Thus, even the absence of enzyme elevation does not exclude the diagnosis.

The typical takotsubo-like picture of the left ventricle can be obtained with echocardiography, contrast ventriculography (Figure 3), or magnetic resonance imaging (MRI) (Figure 4). When available, cardiac MRI can be particularly helpful, since it can also demonstrate the absence of myocardial necrosis on late gadolinium-enhanced images. Indeed, several recent reports of isolated cases or small series underline the role of cardiac MRI as a valuable adjunct in the diagnosis of the underlying disease in patients presenting with chest pain and normal coronary arteries.\textsuperscript{33-35} Moreover, given the well known difficulty in the echocardiographic assessment of right ventricular morphology and function, MRI seems to be the best tool for diagnosing right ventricular involvement in TTC. It is notable that, although right ventricular dysfunction was initially reported only in single cases, more recent reports have shown that this is a rather frequent finding (26-30% of the patients).\textsuperscript{37,38} Finally, a much rarer situation, characterized by a hypercontracting left ventricular apex and a hypokinetic base (the so called inverted takotsubo syndrome), has also recently been described in patients with severe intracranial disease or pheochromocytoma crisis.\textsuperscript{39,40}

A patient with TTC is almost always initially suspected of suffering from an acute coronary syndrome and is referred for urgent or emergency cardiac catheterization. The typical finding is the absence of obstructive coronary artery disease. However, Ibanez et al\textsuperscript{41} were able to describe the presence of ruptured atherosclerotic plaques in some patients with the use of intravascular ultrasound. Whether this finding is of any pathophysiologic relevance remains currently unknown.

Based on their experience and on the current knowledge, a team from Mayo Clinic has proposed some criteria for the clinical diagnosis of TTC (Table 1),\textsuperscript{42} nevertheless acknowledging that exceptions to these criteria also exist.

Management and prognosis

The optimal treatment for TTC remains unknown. Initial management should be definitely directed towards the treatment of myocardial ischemia.\textsuperscript{43} It is extremely important to send the patient immediately to

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Figure 3. Left ventriculogram showing apical dyskinesis (ballooning) in systole (A) and normal systolic function after recovery (B) in a patient with takotsubo cardiomyopathy. (Mohamed HA. Libyan J Med 2007; 2: 51-55, reproduced with permission.)
the catheterization laboratory, since the diagnosis of TTC requires the exclusion of coronary obstructive disease. In addition, a patient who presents acutely with chest pain, ECG changes and left ventricular wall motion abnormalities is far more likely to be suffering from an acute myocardial infarction and should not be denied the benefits of primary angioplasty. For the same reason, aspirin, clopidogrel, nitrates, intravenous heparin and β-blockers should also be started immediately. Close monitoring for the development of heart failure, cardiogenic shock or malignant arrhythmias is also indicated. After the diagnosis of TTC has been established, antiplatelet agents and nitrates should be discontinued. On the other hand, since this is catecholamine-induced clinical syndrome, β-blockers should be kept on board and angiotensin converting enzyme inhibitors should also be started until the recovery of cardiac function. Diuretics are appropriate in the case that congestive heart failure develops. Anticoagulation should also be considered in the case of severe systolic dysfunction to reduce the risk of thromboembolism. If severe hypotension develops, a cautious trial of β-blockers is not appropriate if left ventricular outflow tract obstruction, due to the changes in cardiac geometry in systole, is suspected. However, if pump failure is the cause, inotropes or intra-aortic balloon counterpulsation are indicated. Some authors would advocate for the direct use of intra-aortic balloon counterpulsation and the avoidance of inotropes, since the latter may further deteriorate an already existing intracavitary gradient. Moreover, if catecholamine toxicity is the abnormality directly responsible for the development of TTC, dopamine and dobutamine could, at least in theory, further deteriorate myocardial dysfunction. On the other hand, the calcium-sensitizer levosimendan could be a more appropriate second-line inotropic treatment. Temporary ventricular mechanical support may become necessary in the rare case of life-threatening cardiogenic shock. It should be underlined that none

| 1. Transient akinesis or dyskinesis of the left ventricular apical and mid-ventricular segments with regional wall-motion abnormalities extending beyond a single epicardial vascular distribution |
| 2. Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture |
| 3. New electrocardiographic abnormalities (either ST-segment elevation or T-wave inversion) |
| 4. Absence of: Recent significant head trauma Intracranial bleeding Pheochromocytoma Obstructive epicardial coronary artery disease Myocarditis Hypertrophic cardiomyopathy |

**Figure 4.** Magnetic resonance imaging of the left ventricle in end-diastole (A) and end-systole (B) in a patient with takotsubo cardiomyopathy (our case).
of the above therapies have been tested in clinical trials, and this is also unlikely to happen in the near future given the low prevalence of the disease and its benign course.

Length of treatment has also not been clearly defined. It seems logical to continue treatment until cardiac function has completely recovered.

TTC usually has a benign course with full recovery of left ventricular function within 2-4 weeks from the onset of symptoms in the great majority of the cases. Complications have, however, been described, with the following mean frequency: cardiogenic shock 6.5%, congestive heart failure 3.8%, ventricular tachycardia 1.6%, and death 3.2%. Higher mortality rates up to 21% have nevertheless been reported. Other rare serious complications include ventricular septal defect, left ventricular rupture, apical thrombus formation and stroke.

Conclusions

Takotsubo, or stress cardiomyopathy is an increasingly recognized type of primary acquired cardiomyopathy occurring commonly after a recent stressful event and characterized by transient myocardial systolic dysfunction that is mainly confined to the apical region of the left ventricle. The clinical presentation closely resembles that of an acute coronary syndrome, with chest pain, ischemic type ST-segment changes and minimal cardiac enzyme elevation. Prognosis is good, with full recovery of cardiac function within 2-4 weeks in most of the cases. Treatment is supportive but coronary angiography is necessary to establish the diagnosis. The pathogenetic mechanism remains currently unknown, although catecholamine surge definitely plays a primary role.

References

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