Epidemiology and Clinical Profile of Takotsubo Cardiomyopathy
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Over 25 years, takotsubo cardiomyopathy (TTC) has emerged as a novel and important form of acute cardiac failure characterized by distinctive and reversible left ventricular (LV) contraction abnormalities not mediated by epicardial coronary artery obstruction. TTC was first reported by Dote et al in 1991 in the Japanese language, but was largely unknown or considered obscure until the first reports from Europe and the United States appeared in the late 1990s. From 2001 to 2010, TTC achieved increasing clinical visibility, with reports from Japan, United States, and Europe.

In 2006, the American Heart Association formally recognized TTC as an acquired cardiomyopathy and the number of citations related to TTC has increased dramatically during the past decade from 8 (in 2003) to 246 (in 2013) and now to nearly 2,000 publications. Throughout this time, TTC acquired a variety of names (eg, apical ballooning syndrome, ampulla cardiomyopathy, stress-related cardiomyopathy, broken heart syndrome) most of which describe the unusual end-systolic LV shape and its association with triggering stressful events. The term “takotsubo cardiomyopathy” is now generally accepted in recognition of the initial name that Japanese investigators chose to describe the condition.

Key Words: Myocardial stunning; Takotsubo cardiomyopathy

Epidemiology

Demographic Profile
A common feature of TTC is its propensity to affect older women, often in the postmenopausal years. In the US and Europe, a number of contemporary TTC studies report 90% to 95% of women aged 65–70 years of age. A recent report from a coronary care unit network in Tokyo noted a somewhat older average age of 74 years, which may reflect patient selection and in part the older age of the Japanese population. How- ever, as experience with TTC has expanded, the number of cases reported in younger individuals at virtually any age has increased, including a 2-year-old girl with a malignancy, and also in premenopausal women during pregnancy or childbirth. Notably, TTC in males, once thought to be exceedingly rare, now appears to constitute approximately 10% or more of cases, most commonly as a consequence of a physical stress trigger.

Incidence
Approximately 2% of all patients (10% specifically in women) presenting to the hospital with suspected acute coronary syndrome (ACS) are ultimately identified with TTC. An estimate based on the 2008 Nationwide Inpatient Sample...
Clinical Profiles

Presentation
TTC patients generally present in 2 distinct clinical scenarios: with abrupt onset at home or in the community, or alternatively in a healthcare-related setting during evaluation or treatment of an illness.

Patients with prehospital TTC onset typically present to an emergency department with acute chest pain or dyspnea, symptoms that are often indistinguishable from ACS. Consequently, these patients are usually admitted to a specialized cardiac unit and are often initially treated with aspirin and anticoagulants.

In contrast, TTC onset in healthcare settings occurs in circumstances such as during surgical procedures (eg, orthopedic, abdominal, neurologic, cosmetic, cardiac), with acute medical conditions (eg, sepsis, stroke, malignancy, acute respiratory failure, trauma), or during outpatient procedures (eg, endoscopy, tissue biopsy, chemotherapy, stress testing). In these situations, TTC may manifest as arrhythmia, hypotension, acute pulmonary edema, abnormal ECG, or troponin elevation.

Triggers
A hallmark of TTC is its frequent association with a triggering stressful event. In early reports, most of these events involved emotional trauma. As experience with TTC expanded, a substantial association with physical stressors has emerged. Some specific examples are: laryngeal obstruction from tumor; gastric ulcer with profound hemorrhage; subarachnoid hemorrhage; diverticulitis with septic shock; and diabetic gastroparesis. However, notably, TTC may also occur

Figure 1. Number of patients with takotsubo cardiomyopathy (TTC) compared with ST-segment elevation myocardial infarction (STEMI). Tabulated by year from 2003 to 2013 at Minneapolis Heart Institute. TTC patients: females (n=295), males (n=24); STEMI patients: females (n=1,173), males (n=2,954).
spontaneously (without an overt trigger) in a substantial minority of patients, which has called into question the appropriateness of the common term “stress cardiomyopathy” to describe the overall condition.\textsuperscript{18} In the Minneapolis Heart Institute experience of 337 patients, 10\% of TTC patients provided no history of a stressful event, but physical stressors were present in 50\% and emotional events in 40\%. Indeed, over time, we have observed an emergence of physical events and a decline in emotional events as the identified trigger in these patients. This change is likely related to an increased awareness of TTC occurring during hospitalization for acute noncardiac illness.

The diversity of stressors associated with TTC is striking and ranges from the profound to the mundane (Table).\textsuperscript{7,16,25,39} In some reports, TTC has been linked to conditions that produce high levels of circulating catecholamines, including pheochromocytoma and paraganglioma.\textsuperscript{40,41} Administration of catecholamine drugs (eg, epinephrine, dobutamine) in excessive, or even therapeutic, doses has also been associated with TTC onset.\textsuperscript{42} These observations support the hypothesis that elevated catecholamine levels may be involved in the pathophysiology of TTC.\textsuperscript{12}

<table>
<thead>
<tr>
<th>Table. Diversity of Stressors Triggering Takotsubo Cardiomyopathy Events</th>
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<tbody>
<tr>
<td><strong>Emotional triggers</strong></td>
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<tr>
<td><strong>Anger/frustration</strong></td>
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<tr>
<td>- Heated argument with landlord over rent</td>
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<td>- Argument with husband (afflicted by dementia)</td>
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<td>- Anger and frustration related to organizing a community event</td>
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<td><strong>Financial or employment problems</strong></td>
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<td>- Gambling loss including passing bad checks</td>
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<td>- Personal business failure with loss of life savings</td>
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<td>- Discovery of large business debt</td>
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<td>- Stress during meeting with work manager</td>
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<td>- Stressful beginning to a new job</td>
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<td>- Job loss resulting in need to live in a homeless shelter</td>
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<td><strong>Grief/loss</strong></td>
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<td>- Tenth anniversary of son’s death</td>
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<td>- Found husband unresponsive in driveway after shoveling snow (patient performed CPR)</td>
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<td>- Husband with post-op cardiac arrest and anoxic encephalopathy</td>
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<td>- Withdrawal of life support for brother</td>
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<td>- Advised of son’s death in military</td>
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<td>- Sense of loss after retiring from life-long occupation</td>
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<td>- Impending death of husband from cancer</td>
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<td>- Expressing grief at memorial service for public figure (US Senator)</td>
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<td>- Euthanasia of family dog</td>
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<td>- Reflecting on death of son-in-law during church meeting</td>
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<td><strong>Interpersonal conflict</strong></td>
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<tr>
<td>- Lengthy divorce culminating in sale of home of 28 years</td>
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<tr>
<td>- Separation from husband</td>
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<td>- Severe depression with suicidal ideation</td>
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<td>- Failure to keep up with daughter during bicycle race</td>
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<td>- Altercation with mentally ill daughter</td>
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<td>- Discussing brother’s methamphetamine addiction and alcoholism</td>
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<td>- Relocation of permanent residence</td>
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<td>- Physical domestic abuse by spouse</td>
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<td>- Estrangement from daughter</td>
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<td>- Overwhelming emotion during 50th wedding anniversary</td>
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<td>- Informed that best friend moving great distance</td>
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<td>- Upsetting phone call from friend</td>
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<td>- Sexual abuse by relative</td>
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<td>- Disclosure that unmarried daughter is pregnant</td>
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<td>- Loss of child custody</td>
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- **Panic/fear/anxiety**
  - Flat tire while driving a remote road without cell phone
  - Accidental fall outdoors during Minnesota winter with hip fracture (feared freezing to death)
  - Legal deposition regarding motor vehicle accident
  - Lost while driving in unsafe neighborhood at night
  - Frightened by alarm signal from carbon monoxide monitor
  - Lost with flat tire while driving mother to physician appointment
  - Poultry barn burned down (fearing loss of chickens)
  - Anxiety regarding a public speaking event
  - Sudden illness of husband
  - Basement flood during intense thunderstorm
  - Anxiety about elevated blood pressure
  - Anxiety about elective cardioversion for atrial fibrillation
  - Panic while trying to load store purchases into car during bitter cold
  - Fall at home while alone with fear of not being found
  - Fall at home with hip fracture; unable to call for help
  - Panic attack during lung biopsy for suspected malignancy
  - Caught in storm on pontoon boat
  - Identity theft
  - Flooding of home from frozen and burst water pipes

- **Physical triggers**
  - Acute respiratory failure
    - Chronic obstructive pulmonary disease exacerbation (some with bronchodilator use)
    - Pulmonary embolism
    - Laryngeal obstruction from neoplasm
    - Respiratory distress from influenza
    - Acute epiglottitis (\textit{Pasteurella multocida}) requiring intubation

- **Central nervous system conditions**
  - Subarachnoid hemorrhage
  - Brain contusion from accidental fall
  - Ruptured cerebral aneurysm
  - Vasculitis
  - Migraine headache treated with zolmitriptan
  - Seizure
  - Brain abscess
  - Vertebral artery dissection with stroke

- **Malignancy**
  - Chemotherapy for esophageal cancer
  - Metastatic carcinoid tumor
  - Adenocarcinoma of lung metastatic to brain
  - Chemotherapy for metastatic colon cancer
  - Advanced cervical sarcoma
Circulation Journal Vol.78, September 2014

Other common ECG patterns in TTC include: diffuse T-wave inversion, anterior Q waves, and left bundle branch block. The 12-lead ECG on presentation is abnormal in most TTC patients. MI with minimal biomarker release, considered a manifestation of TTC, is present in approximately 25% of patients. The unique end-systolic apical ballooning configuration reminded Japanese physicians of the takotsubo, a subspherical pot used to trap octopus, leading to the distinctive name based on the angiographic configuration. In the occasional patient, the TTC apical ballooning pattern is similar to the contraction abnormality caused by ischemia from significant LAD coronary artery stenosis, which extends beyond the LV apex to supply the inferior wall ("wrap-around" LAD).

Ventricular Contraction Patterns

To date, 3 unique patterns of abnormal LV contraction have been identified, classified as apical, mid, and basal ballooning (Figure 4). In each, the LV wall motion abnormality is circumferential and distinct from that caused by obstructive coronary artery disease. LV apical ballooning pattern was the first to be described as characteristic of TTC, and is present in approximately 75% of patients. The unique end-systolic apical ballooning configuration is rare and encountered in only 1%. There does not appear to be any particular clinical significance attached per se to these distinctive contraction patterns.

Segmental wall motion abnormalities involving the apical right ventricle are identifiable with echocardiographic or cardiac magnetic resonance (CMR) imaging in 25% of patients, and are observed with either LV apical or mid-ventricular ballooning, although a few case reports suggest it can occur in isolation. In some reports, right ventricular dysfunction has been a marker for TTC severity and associated with hemodynamic instability and HF, lower ejection fraction, and longer hospital stay.

Cardiac Stunning

From its initial description, a dramatic and characteristic hallmark of TTC has been the complete reversibility of left (and right) ventricular contraction abnormalities and symptoms within days to weeks, although delayed recovery of 1–2 months has been reported in a few patients. Longer persistence of LV systolic dysfunction (beyond 2 months) should prompt consideration for a coexisting cardiomyopathy. In TTC, the almost universal absence of delayed gadolinium enhancement on CMR in the region of abnormal LV contraction indicates tissue viability and may explain myocardial recovery in TTC.

Abnormalities of myocardial perfusion, sympathetic nerve
Heart Failure in TTC

TTC is a novel form of acute HF characterized by abrupt loss of regional LV contractile function involving a substantial myocardial mass. Ejection fraction is acutely reduced to 30–35%, and below that observed during acute anterior MI, likely because of a larger mass of akinetic myocardium (Figure 6). LV stroke work is 50% of normal, with markedly increased end-systolic volume reflecting major impairment of LV pump function and leading to reduction in stroke volume and cardiac output.

Furthermore, LV diastolic function is also acutely disturbed, with an upward shift in the LV diastolic pressure-volume curve, resulting in substantially elevated LV end-diastolic pressure without significant increase in LV end-diastolic volume. Under these circumstances, TTC patients may experience clinically important hemodynamic instability, including profound hypotension (requiring intervention with inotropic drug therapy and/or intra-aortic balloon pump [IABP]), pulmonary edema, and cardiogenic shock. A recent Italian report of 227 patients noted acute HF (pulmonary edema and/or oxygen desaturation requiring intervention) in 20% and cardiogenic shock in 8%, and a TTC registry from Germany and Austria (324 patients) reported pulmonary edema in 8% and cardiogenic shock in 4%. In our 337 TTC patients at the Minneapolis Heart Institute, 15% had unstable hypotension requiring inotropic drugs or IABP, two-thirds of whom had acute pulmonary edema or cardiogenic shock. Taken together,
**Figure 3.** Occurrence of torsade de pointes (TdP) ventricular tachycardia in an 84-year-old woman with an apical ballooning takotsubo cardiomyopathy (TTC) event triggered by emotional stress. **(Top)** Admission ECG demonstrates sinus bradycardia, prominent T-wave inversion, and QTc prolongation to 549 ms. **(Bottom)** Continuous 18-s recording of lead II rhythm strip 2 h after admission shows sinus bradycardia with paired premature ventricular contractions followed by TdP ventricular tachycardia, which self-terminated. The patient received a permanent pacemaker for underlying sinus node dysfunction and TdP resolved with higher heart rate.

**Figure 4.** Diversity of left and right ventricular contraction patterns in takotsubo cardiomyopathy (TTC) demonstrated by cardiac magnetic resonance imaging in the horizontal long-axis view at end-systole. **(A)** Apical ballooning with akinesia in mid- and apical left ventricular (LV) segments (arrows); **(B)** mid-ventricular ballooning with akinesia in only the mid-LV segments (arrows); **(C)** basal ballooning with akinesia in basal LV segments (arrows); **(D)** RV apical dyskinesia (thin arrows) associated with LV apical ballooning (arrows). Adapted with permission from Sharkey SW. 52
Figure 5. Myocardial contractile and perfusion stunning in takotsubo cardiomyopathy (TTC) in a 55-year-old woman with emotional stress-induced apical ballooning. Serial single-photon emission computed tomography (SPECT) images at rest show left ventricular (LV) ejection fraction (EF) and LV perfusion map in a polar plot display (normal perfusion is depicted in bright orange-white and abnormal perfusion in black). (Top) Initial study: EF is 29% with circumferential LV perfusion defect not corresponding to a single coronary artery distribution. (Middle) At 48 h: EF improved to 47% and the LV perfusion defect is substantially smaller. (Bottom) At 96 h: LVEF and perfusion have both normalized. Adapted with permission from Sharkey SW.52

Figure 6. Distribution of ejection fraction (EF) on admission for takotsubo cardiomyopathy (TTC) compared with ST-segment elevation myocardial infarction (STEMI). (Top) TTC in 330 consecutive patients. (Bottom) STEMI in 3,954 consecutive patients. As a group, the EF in TTC is significantly lower than in STEMI: 32±11% vs. 47±14%, respectively, P<0.001.
In addition to reduced LV ejection fraction, several additional factors potentially contribute to hemodynamic instability, including local myocardial edema (present in up to 80% on magnetic resonance imaging) leading to impaired LV compliance, or dynamic LV outflow tract obstruction and mitral regurgitation secondary to systolic anterior motion of the mitral valve (in 10–20% of patients) (Figure 7). Subaortic obstruction is more common with the apical ballooning pattern, may be provoked or exacerbated by catecholamine drugs used to treat hypotension, and is associated with mitral regurgitation. Persistence of mitral valve systolic anterior motion and outflow tract obstruction (with septal hypertrophy) after recovery may indicate coexisting hypertrophic cardiomyopathy. Isolated acute reversible mitral valve regurgitation has been reported in 20% of TTC patients and is associated with acute pulmonary edema and cardiogenic shock.

**Outcome**

Although initially regarded as an almost uniformly benign and reversible condition, it is now evident that TTC carries with it a not inconsequential risk for adverse outcome.

**Arrhythmias** Life-threatening arrhythmias are part of the clinical spectrum of TTC (in ~2% of patients), including ventricular fibrillation, torsade de pointes ventricular tachycardia, pulseless electrical activity, and asystole on presentation or during hospitalization. In patients experiencing cardiac arrest, it may be uncertain whether TTC should be incriminated as the cause or alternatively the consequence of the arrhythmia. The profound stress of cardiac arrest and subsequent resuscitation (sometimes with administration of epinephrine) can itself trigger a TTC event. Furthermore, a catastrophic non-TTC medical event (eg, acute respiratory failure or intracranial hemorrhage) could potentially cause cardiac arrest associated with TTC.

Torsade de pointes occurs in a subset of TTC patients in the setting of QT prolongation, typically >500 ms (Figure 3). Male patients and those patients with bradycardia, heart block, and atrial fibrillation appear to be more susceptible. Because lengthening of the QT interval may occur after onset of the event, it is prudent to continue rhythm monitoring at least until hospital discharge; drugs that promote QT prolongation should be used judiciously or avoided.

In our Minneapolis Heart Institute TTC cohort, occurrence of cardiac arrest was 4%, which exceeds that reported in the literature and may reflect increased awareness of TTC or the establishment of a local therapeutic hypothermia program resulting in increased referrals to our hospital. In one-half of these patients, a major noncardiac event (acute respiratory failure or chronic obstructive lung disease, subarachnoid hemorrhage) immediately preceded the cardiac arrest. However, in the other patients the TTC event itself was the only identifiable substrate for cardiac arrest, and each of these patients received a secondary prevention implantable defibrillator. Taken together, these observations raise the possibility that TTC may be a cause of unexplained sudden death in older patients.

**Embolic Events** Akinetic segments within the left and right ventricles provide the substrate for endocardial thrombus formation. Ventricular thrombi may be present in approximately 5% of TTC patients, may be multiple, and located at sites distinctly different from those in acute MI and can lead to systemic and pulmonary embolic events (Figure 7). CMR has proven to be more sensitive than 2-dimensional echocardiography for detection of ventricular thrombi in TTC and anticoagulation should be considered until the risk of thrombus has resolved associated with normalized myocardial contraction.

**In-Hospital Mortality** Hospital mortality in TTC is low despite the severity of acute HF and LV systolic dysfunction, and >95% of patients experience complete cardiac recovery.
In the Minneapolis experience, 97% of TTC patients survived to hospital discharge (including several who experienced pulmonary edema or cardiogenic shock as complications), with ejection fraction increasing from 32% on admission to 57% at follow-up. All in-hospital TTC deaths came from a high-risk subgroup comprising patients with cardiac arrest or marked arterial hypotension requiring intravenous vasopressors and/or IABP. Notably, each nonsurvivor also had an irreversible noncardiac condition (e.g., subarachnoid hemorrhage, acute respiratory failure, malignancy) with the potential to compromise clinical status and adversely influence short-term survival. Other investigators have also noted the importance of such coexisting noncardiac conditions affecting hospital survival. Large TTC patient registries have reported in-hospital mortality of 2% in Germany and Austria (n=324), and 3% in Italy (n=227), and 4% in the US National Inpatient Sample (n=24,701), as well as an 11-country survey (n=2,120). LV free wall rupture and ventricular septal defect are known complications leading to TTC-related death.

Post-Hospital Survival Assessments regarding long-term post-TTC survival are limited and unavoidably influenced by the older age of this patient population. Our experience supports higher all-cause mortality for TTC compared with the age- and sex-matched general population. Excess mortality occurred predominantly within the first year after the TTC event, usually because of malignancy or noncardiac conditions. In contrast, in a relatively small study, post-hospital survival at 4 years did not differ significantly from that of an age- and sex-matched general population.

Recurrent TTC events may recur in 5–10% of patients and appear as early as 3 weeks or as late as 4 years after the initial event. Repeated or serial TTC has been encountered. We have treated 2 female patients who have experienced repeat TTC events between 2003 and 2012, of which 5 were triggered by an emotional stressor. Notably, in patients with recurrent TTC, the LV ballooning pattern may differ; for example, with apical ballooning during the initial event and mid-ventricular ballooning during the second event. Initial and recurrent TTC events have been reported in patients receiving β-blocker therapy, typically administered for coexisting systemic hypertension. In our cohort, 18% of patients were receiving β-blocker drugs at the time of their initial TTC event, and 43% at the time of a recurrent episode.

Based on this observational evidence it would appear that β-blockers are not absolutely protective against TTC.

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