Takotsubo Cardiomyopathy

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★ ***CME Credit***

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Takotsubo cardiomyopathy (TC) is also known as stress cardiomyopathy, transient left ventricular (LV) apical ballooning syndrome, neurogenic myocardial stunning, and broken-heart syndrome.[1] The term takotsubo was first used by Sato and colleagues[2] in 1990 because of similarities between the morphologic features of the LV (when affected by TC) and the shape of a Japanese octopus trap. A common occurrence among cases of TC is a stressful event that serves as a trigger.[3]

In 70% to 80% of cases, the cardiomyopathy is characterized by transient LV systolic dysfunction with apical akinesis or dyskinesis (apical ballooning) and compensatory basal hyperkinesis in the absence of obstructive coronary artery disease (CAD).[3] The other 20% to 30% of cases are atypical forms that involve either basal or midventricular hypokinesis with apical sparing.[4] In "reverse takotsubo" (1%–2% of cases), the basal segments are hypocontractile or akinetic, compared with the hypercontractile apical segments. An additional finding in some patients is right ventricular (RV) involvement, usually concomitant with typical left ventricular TC (Fig. 1).[1]

Pathophysiology

A marked hyperadrenergic state appears to be a common thread in TC cases.[3,5,6] Hypotheses to explain the transient and reversible apical dysfunction include aborted myocardial infarction with spontaneous recanalization, acute microvascular dysfunction, multivessel coronary vasospasm, acute LV outflow tract obstruction, and direct catecholamine-mediated myocardial dysfunction. Catecholamine excess could cause direct myocardial toxicity or induce microvascular dysfunction or coronary spasm.[7] Variable distribution and density of cardiac beta-1 and beta-2 receptors throughout the myocardial segments has been postulated to explain the observed segmental wall-motion abnormalities, which do not correspond to typical coronary artery distributions but instead might correlate with beta-receptor distributions.[7]

Endothelial dysfunction as evoked by intracoronary acetylcholine or ergonovine injection is detected in up to 10% of studied cases, but whether endothelial hyperreactivity causes TC or results from another primary mechanism is not clear.[8,9] In addition, the diagnostic or therapeutic usefulness of routine vasoreactivity testing has not been clearly established. Coronary flow reserve testing is another potentially promising technique for better understanding the pathophysiology of TC. Patel and colleagues[10] calculated coronary flow reserve by injecting intracoronary acetylcholine into 10 patients with TC; the investigators determined that the acetylcholine either decreased coronary blood flow or induced epicardial vasoconstriction in 90% of patients. Similarly, Thrombolysis In Myocardial Infarction (TIMI) frame count can be prolonged in all 3 major epicardial coronary vessels in the acute setting, which suggests that there is diffuse impairment of coronary microcirculatory function.[11]

Triggers

Emotional stressors that have been described in the medical literature include the death, severe illness, or injury of a loved one, the receipt of bad news, a severe argument, an assault, public speaking, financial loss, a car accident, and natural disasters.[1,12] There might be social or cultural differences in the types of emotional stressors that trigger TC and in patients' willingness to report the sources of stress, but these possibilities have not been formally studied to date.[13]

Physical stressors that have been reported include surgical procedures such as cholecystectomy, colonoscopy, difficult urinary catheterization, pacemaker implantation, and electrical cardioversion.[1,6,9] Physical stressors are observed more often in male pa-

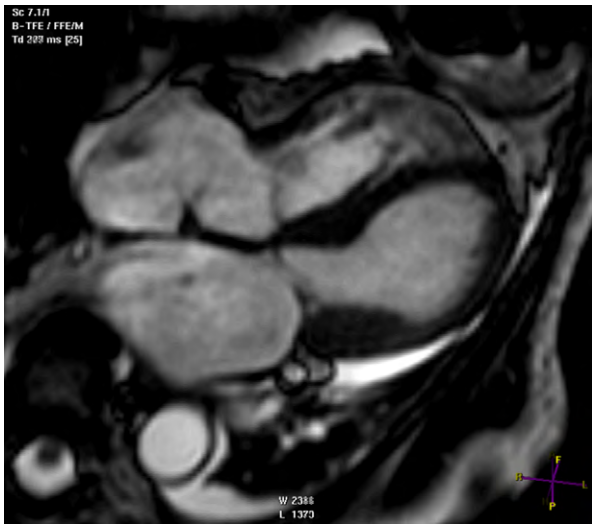

Fig. 1 *Cross-sectional gated cardiac magnetic resonance image shows right ventricular and left ventricular akinesis (biventricular takotsubo).*

Supplemental motion image is available for Figure 1.

tients (57%), while emotional triggers are more commonly seen in female patients.[14]

Medical conditions that can lead to TC include asthma exacerbation, acute pancreatitis, sepsis, and severe hypothyroidism.[1] Neurologic events such as subarachnoid hemorrhage can be associated with midventricular or reverse takotsubo.[15,16] In these cases, the elevation in troponin I is modest.[17] Notably, the absence of a precipitating factor does not preclude the diagnosis of TC, because one third of patients do not have identifiable triggers.[1]

Patient Demographics

Ninety percent of patients diagnosed with TC are women.[18] In fact, most TC patients are postmenopausal women 61 to 76 years of age.[12]

In Western countries, retrospective data show that 2% to 3% of patients suspected of having an acute coronary syndrome are eventually diagnosed with TC.[14] Newer prospective studies of women presenting with acute coronary syndrome criteria suggest a prevalence of TC as high as 6%.[19]

Clinical Presentation

Takotsubo cardiomyopathy mimics acute coronary syndrome. Chest pain and dyspnea are the most frequent presenting symptoms. Acute heart failure can occur in up to 45% of patients.[1] Rarely, patients present with nausea and vomiting, syncope, and ventricular fibrillation.[14]

Diagnostic Criteria

The Mayo Clinic diagnostic criteria for TC include the following[3,6]:

1) Transient hypokinesis, akinesis, or dyskinesis of the LV mid segments with or without apical involvement; regional wall-motion abnormalities beyond a single epicardial coronary distribution; and, often, a stressful trigger.
2) Absence of obstructive coronary artery disease or angiographic evidence of acute plaque rupture.
3) New electrocardiographic (ECG) abnormalities (ST-segment elevation, T-wave inversion, or both) or modest elevation in cardiac troponin levels.
4) Absence of pheochromocytoma or myocarditis.

The most frequent finding on presenting ECGs is ST-segment elevation in the precordial leads; however, ST elevation can occur in any leads (Fig. 2).[14,20] Over time, the ST-segment elevation subsides and is replaced by widespread T-wave inversion. Patients with TC often have QT prolongation, which typically resolves within 3 to 4 months.[3]

Serum levels of cardiac biomarkers, including creatine kinase and troponin, are often elevated in patients with TC, albeit not as much as in patients with acute myocardial infarction.[14,20,21] Takotsubo cardiomyopathy appears to be infrequent in patients with troponin T levels greater than 6 ng/mL or troponin I levels greater than 15 ng/mL.[21] Brain natriuretic peptide levels are also elevated in TC patients, but to a much lesser extent than would be expected from patients presenting with heart failure who have a similarly low ejection fraction.[3]

Ultimately, the main feature that distinguishes TC from other cardiac disorders such as acute coronary syndrome, syndrome X, coronary vasospasm (variant angina), and myocarditis is the rapid recovery of LV function.[22]

Sex Differences

Takotsubo cardiomyopathy disproportionately occurs in postmenopausal women.[12] Because TC can occur in

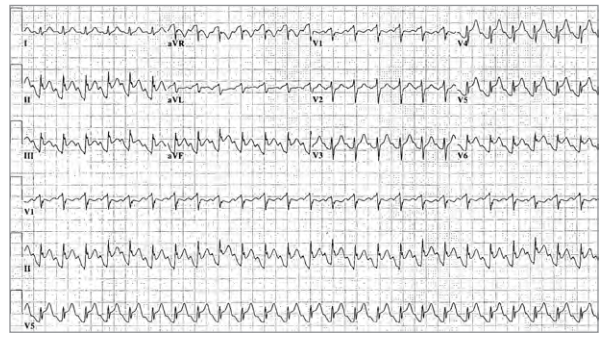

Fig. 2 *Electrocardiogram shows ST-segment elevation in the inferolateral leads in a 71-year-old patient who developed takotsubo cardiomyopathy after sustaining a spontaneous pneumothorax.*

Figures 3–7 show other aspects of this same case.

males and in younger females, the Mayo Criteria intentionally omit age and sex.[3] As previously mentioned, the identifiable triggers for TC in women usually include emotional stress, whereas TC in men is usually triggered by physical stress.[14] Men are more likely to have out-of-hospital arrest, elevated cardiac biomarkers, and evidence of prolonged QT interval on ECG. In contrast, women are more likely than men to have chest pain.

Additional Evaluation, Testing, and Imaging Techniques

Cardiac catheterization usually shows normal coronary arteries (Fig. 3). Obstructive CAD can be excluded only if luminal stenosis is less than 50%.[14] Left ventriculography reveals apical ballooning in 60% of cases and a midventricular ballooning pattern with apical sparing in the other 40%.[3] In up to 10% of cases, mild or moderate CAD can be detected, and in many cases, the coronary arteries have new luminal abnormalities.[23] Typically, the TIMI flow grade is also reduced.

At presentation, patients with TC are essentially indistinguishable from those with ST-elevation myocardial infarction. Therefore, all patients with signs and symptoms of these 2 conditions should be taken to the cardiac catheterization laboratory. Takotsubo cardiomyopathy can be diagnosed retrospectively only if there is no angiographically significant CAD and there is apical hypokinesis or akinesis that suggests TC (Fig. 4).

Early evaluation of LV systolic function, either by dedicated LV angiography or by echocardiography, is essential for the diagnosis. Echocardiography shows characteristic wall-motion abnormalities, including apical hypokinesis or akinesis and basal hyperkinesis (Figs. 5 and 6). Associated findings can include ventricular thrombus, dynamic LV outflow tract obstruction, mitral regurgitation, and RV enlargement and dysfunction (Fig. 7). Echocardiography is also useful in documenting recovery, usually showing the return of normal ejection fraction in 6 to 8 weeks.[1,12] However, improvement is frequently seen in a much shorter time.

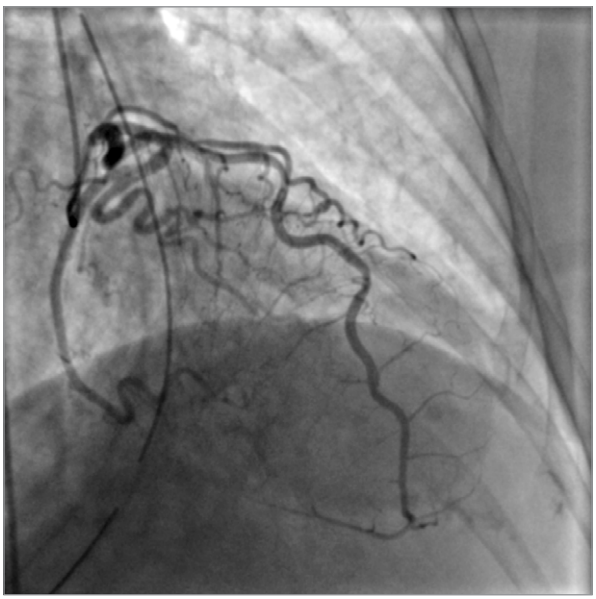

Fig. 3 *Coronary angiogram shows normal coronary arteries in the same patient (Fig. 2).*

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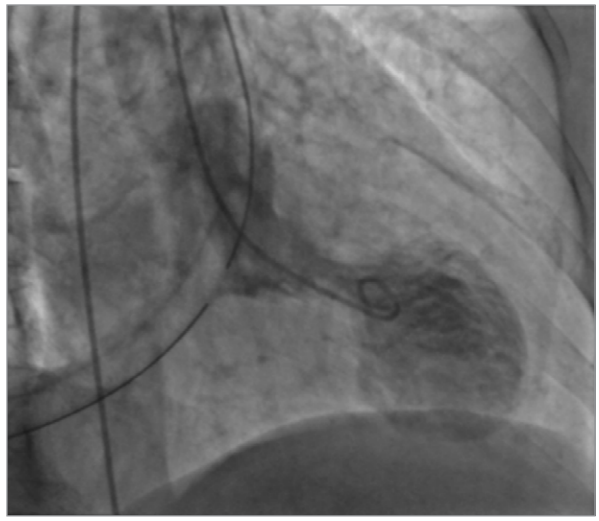

Fig. 4 *Left ventriculogram shows apical akinesis in the same patient (Fig. 2).*

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Cardiac magnetic resonance imaging (MRI) can be helpful as a second-line imaging modality in patients with suspected TC but poor echocardiographic windows, or when it might be useful to confirm the presence of viable myocardium in the akinetic regions. Cardiac MRI can also detect LV dysfunction in a non-coronary regional distribution pattern with or without RV involvement, myocardial edema in the segments with wall-motion abnormalities, and the absence of high-signal areas.[5] Several MRI findings are useful for differential diagnosis, including intense delayed subendocardial or transmural hyperenhancement in acute myocardial infarction, patchy hyperenhancement in myocarditis, and edema in TC.

Nuclear imaging sometimes reveals a defect extending beyond a single coronary artery distribution, corresponding to the area of abnormal LV contraction. These changes can be seen during the acute phase of TC; subsequent imaging shows gradual resolution of the perfusion defects (Fig. 8).[24]

Treatment

Short-term therapy involves supportive care and targeting the precipitating trigger if it is known.[22] Further treatment usually involves standard heart-failure therapy, such as angiotensin-converting enzyme (ACE) inhibitors and beta-blockers. In cases of cardiogenic

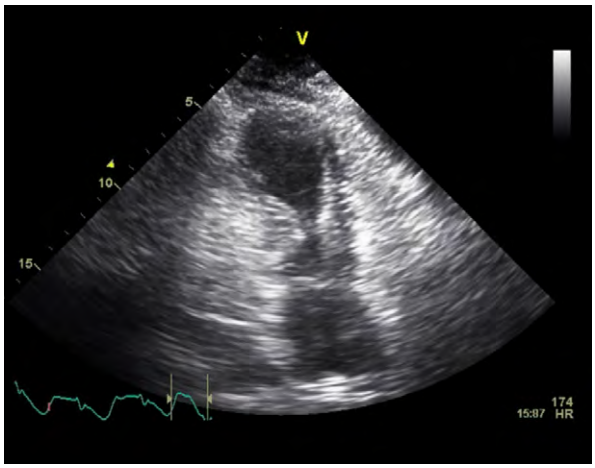

Fig. 5 *Echocardiographic apical 2-chamber view shows apical akinesis and a hypercontractile base in the same patient (Fig. 2).*

Supplemental motion image is available for Figure 5.

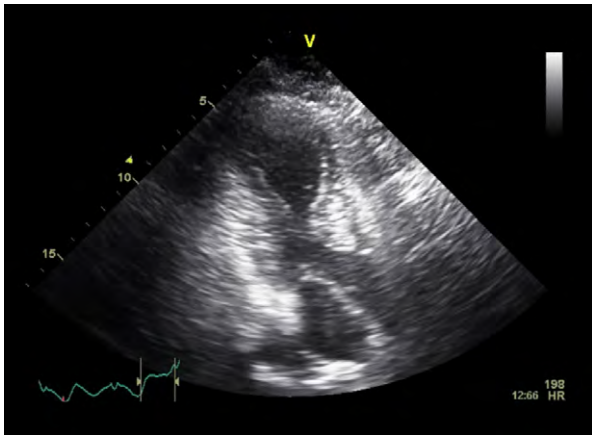

Fig. 6 *Echocardiographic apical 3-chamber view shows apical akinesis and a hypercontractile base in the same patient (Fig. 2).*

Supplemental motion image is available for Figure 6.

shock, intra-aortic balloon pumps can be placed.[1] Inotropic agents should be avoided, because they can worsen or precipitate dynamic LV outflow tract obstruction and might exacerbate hyperadrenergic activity, which could be causal. Patients who have LV thrombus require anticoagulation.

After recovery, ACE inhibitors can be discontinued when the LV returns to normal. Beta-blockers can be continued on the theoretical grounds that they could prevent recurrence.[1,22]

Prognosis

Prognosis in TC is generally very good. However, monitoring for early dangerous complications is essential.[22] In-hospital mortality rates range from 0 to 8%. The risk of recurrence is low and was reported to be 10% over a 4-year period in one report.[25]

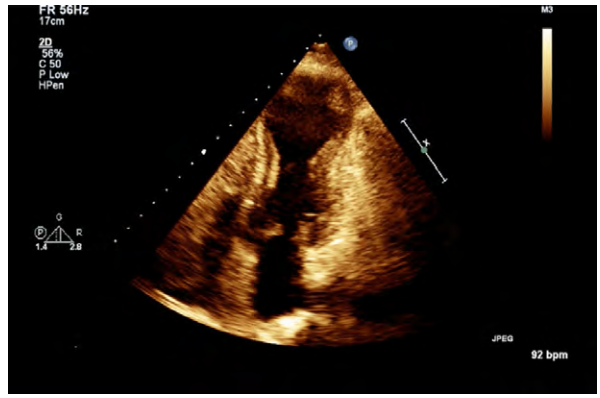

Fig. 7 *Apical 2-chamber echocardiographic view shows left ventricular thrombus in the same patient (Fig. 2).*

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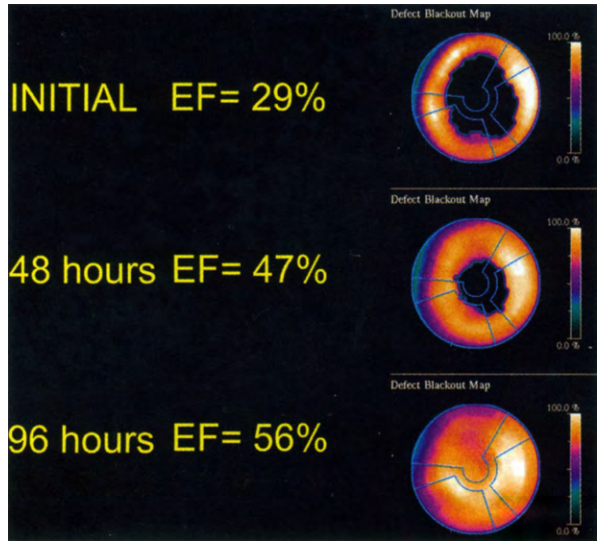

Fig. 8 *Serial single-photon emission computed tomographic left ventricular polar maps with corresponding left ventricular ejection fractions (EF) at 0, 48, and 96 hours.[24] Reprinted from Heart Fail Clin 2013;9(2):123-36, vii. Sharkey, SW. Takotsubo cardiomyopathy: natural history. Copyright (2013), with permission from Elsevier and SW Sharkey.*

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