Reviews

An Unusual Manifestation of Tako-tsubo Cardiomyopathy

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ABSTRACT

Tako-tsubo cardiomyopathy (TC) typically presents with chest pain, ST changes, and transient left ventricular (LV) apical ballooning in the absence of epicardial coronary artery disease (CAD). This process is reversible and usually benign. An unusual manifestation is that of left ventricular outflow tract (LVOT) obstruction with systolic anterior motion of the mitral valve. Recognition of this finding is critical in patient management especially in the setting of cardiogenic shock, as inotropes are likely to aggravate and worsen the clinical condition. We provide a systematic review and an illustrative case, and discuss treatment strategies.

Key words: tako-tsubo cardiomyopathy, left ventricular outflow tract obstruction, coronary vasospasm, left ventricular apical ballooning

Tako-tsubo cardiomyopathy (TC) mimics acute myocardial infarction (MI) and should be considered in all patients, especially post-menopausal women who present with transient left ventricular (LV) dysfunction in the absence of obstructive coronary artery disease (CAD). Approximately 2% of all patients presenting with a presumed diagnosis of ST segment elevation MI have this syndrome,[1] and 87% of the reported cases of TC are post-menopausal women with a mean age of 68.[2]

While TC frequently presents with substernal chest pain, these patients might present with electrocardiogram (ECG) changes alone, shortness of breath, or cardiogenic shock.[3] The ECG changes include ST elevation, ST depression, T-wave inversion, pathologic Q waves, and QT prolongation.[2] New left and right bundle branch blocks have been reported,[4] but the most common ECG changes are ST elevation (68%), which is most commonly seen in the precordial leads and diffuse T-wave inversions (97%).[2,4] The frequency of ST depression and Q waves is ~10% and 27%, respectively.[3–5]

There is usually mild elevation of troponin, and less commonly, creatine kinase (CK) and its isoenzyme CK-MB, but the pattern differs from that seen following MI. In fact, cardiac enzyme levels peak at the onset of symptoms, and they do not slowly rise and fall as in MI.[2,4] Troponin and CK-MB levels are elevated in 86% and 74% of the cases, respectively.[6]

Several LV wall motion abnormalities have been described in the setting of TC. The classic abnormality involves ballooning of the distal LV segments and apex as a result of severe hypokinesia, akinesia, or dyskinesia. At the same time, there is compensatory basal hyperkinesia. A less common variant involving mid-LV dyskinesia has also been described.[7] These transient LV wall motion abnormalities can be detected by left ventriculography, 2-Dimensional echocardiography (2DE), gated single photon emission computed tomography (SPECT), and magnetic resonance imaging (MRI), and usually involve multiple vascular territories.[8]

The pathophysiology behind TC is poorly understood. However, according to a recent large systematic review of 542 cases, physical or emotional stress precipitated the reversible LV dysfunction in ~80% of the cases.[2] Excessive sympathetic stimulation, vascular abnormalities, and metabolic disturbances have been suggested as being responsible.[2,9]

We present a patient with TC and hemodynamic compromise with 2 unusual manifestations, severe LV outflow tract (LVOT) obstruction with systolic anterior motion of the mitral valve, and spontaneous right coronary vasospasm.

Case Summary

A 70-year-old Caucasian woman presented to a community hospital complaining of substernal chest pressure associated with nausea and presyncope for ~60 min.

Past medical history was notable for hypertension, hypothyroidism, and gastroesophageal reflux disease. The patient does not smoke and has no family history of CAD. She had a stress sestamibi study ~7 mo earlier for atypical chest pain, which showed normal perfusion and normal LV ejection fraction (EF) of 73%.

On examination, she was ill-appearing, diaphoretic, and afebrile. The heart rate was 83 beats/min, blood pressure was 97/72 mmHg, and respiratory rate was 16 breaths/min. The jugular venous pressure was 8 cm with normal waveforms, and the carotid upstroke was mildly diminished.

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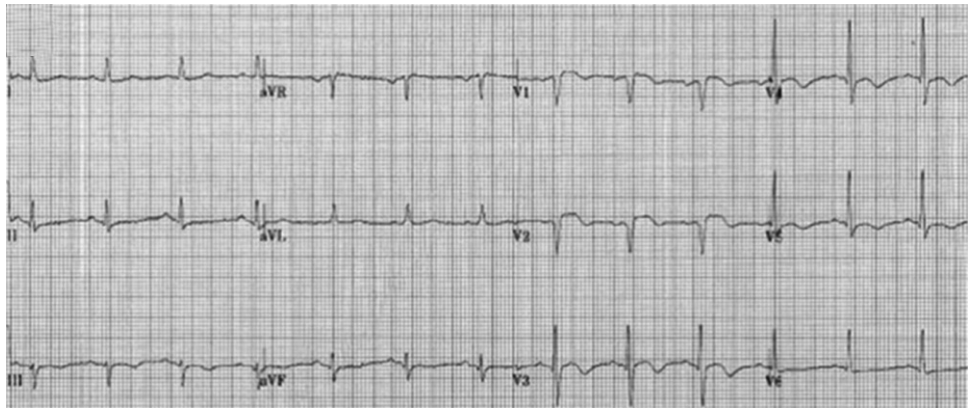
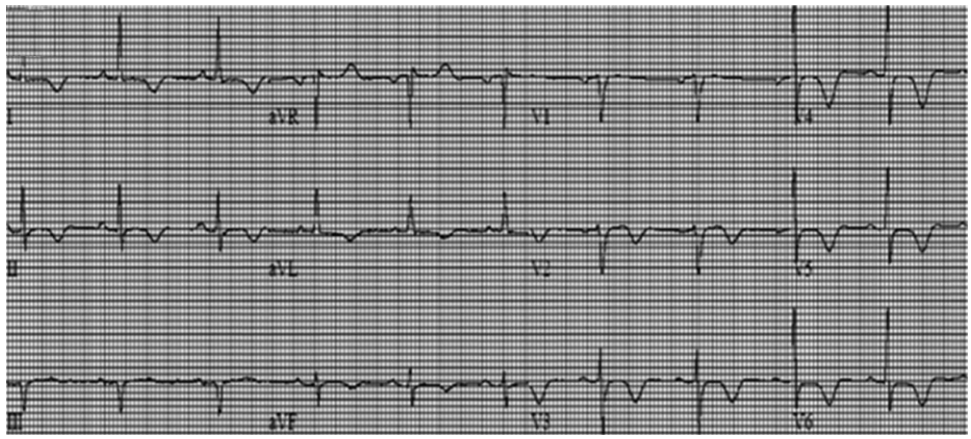


(A)



(B)

Figure 1: (A) The ECG at presentation with substernal chest pressure is significant for 1 mm of ST segment elevation in V1–V2, septal Q waves, and diffuse T-wave inversions. (B) The ECG prior to discharge revealed normal sinus rhythm and diffuse T-wave inversions without Q waves or ST changes.

She had a nondisplaced point of maximal impulse with no lifts, heaves, or thrills. S1 and S2 were normal. An S3 and a soft II/VI holosystolic murmur were audible at the apex with radiation to the axilla. The respiratory and abdominal examinations were unremarkable, and there were no clubbing, cyanosis, or edema.

Initial ECG revealed normal sinus rhythm with septal Q waves with ~1 mm of ST elevation in V1–V2 and diffuse T-wave inversions (Figure 1). Initial serum cardiac troponin level was elevated at 0.25 mg/dL (upper limit of normal = 0.09 mg/dL), and total CK was 215 with a CK-MB fraction of 26.

Two-Dimensional echocardiography revealed a thick proximal septum with a sigmoid appearance, dyskinesia of the mid- and distal-septal and anterior walls, and apical dyskinesia (Figure 2). There was LVOT obstruction (gradient ~35 mmHg) with systolic anterior motion of the mitral valve and moderate mitral regurgitation (Figure 3).

A cardiac catheterization was performed that revealed no significant obstructive CAD, but there was severe right coronary artery spasm that resolved with intracoronary nitroglycerin (Figure 4). Left ventriculography revealed LV apical ballooning with an EF of ~35% (Figure 4). Aortic pressure was 90/50 mmHg, and LV pressure was 147/13 mgHg prior to the A wave and 147/25 mmHg post A wave. The LVOT gradient was 50 mmHg (Figure 4). Pulmonary artery pressure and pulmonary artery capillary wedge pressure were 37/15 mmHg (24) and 24 mmHg, respectively.

After ~7 d of hemodynamic support including dobutamine and neosynephrine for cardiogenic shock, the patient was transferred to the University of Alabama at Birmingham for consideration of heart transplant evaluation and further management including a consideration for myomectomy or ethanol ablation for a presumed diagnosis of hypertrophic obstructive cardiomyopathy (HOCM). A 2DE was done on

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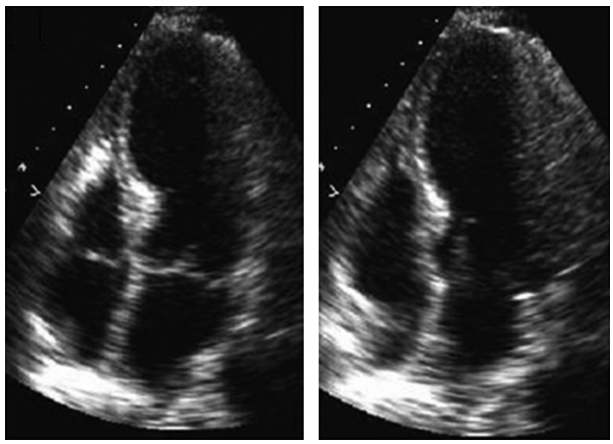

(A) (B)

Figure 2: Two-Dimensional ECG. Apical 4-chamber view in (A) end diastole and (B) end systole, revealing LV apical ballooning.

arrival that revealed, however, normal LV and right ventricular function and normal wall motion. There was no underlying asymmetric septal hypertrophy present in this patient separate from the acute event, and there was no LV outflow gradient at rest and only 10 mmHg after amyl nitrate. Velocity was 1.6 m/s. Adenosine-gated SPECT myocardial perfusion images were obtained 11 d after her initial presentation, and the perfusion images were normal; the LVEF was 60%, and there were no wall motion abnormalities.

This case provides evidence of 2 unusual manifestations of TC, coronary artery vasospasm and LVOT obstruction.

Patients with TC have a favorable prognosis and rapidly improve within days to weeks.[4,6] While chest pain is the most common presentation, left-sided heart failure occurs in ~22% of patients, and intra-aortic balloon pump (IABP) counterpulsation is required in ~8% of cases.[3] Several severe but rare presentations have been described, such as cardiogenic shock, ventricular arrhythmias, LV free wall rupture, LV thrombus, mitral regurgitation, LVOT obstruction with systolic anterior motion of the mitral valve, and death.[1,3,4,10] In-hospital mortality is <1%, and TC rarely reoccurs.[4,6]

As of March 4, 2007 there have been ~605 cases of TC reported in the English literature, and to our knowledge, only 12 (2%) patients have presented with transient LVOT obstruction (Table 1). However, dynamic intraventricular pressure gradients have been reported in 13–23% of cases.[6] Mitral regurgitation from systolic anterior motion of the mitral valve leaflet can occur, but the frequency is unknown.[4]

Left ventricular outflow tract obstruction is generally seen in the setting of HOCM, but it has also been described in patients with acute coronary syndromes and severe emotional stress. In fact, Villareal et al. reported 3 female patients presenting with chest pain, anteroapical stunning, and LVOT obstruction following excessive sympathetic stimulation.[10] Although they attributed the myocardial stunning to large vessel spasm, these cases are consistent with TC.

Transient dynamic LV intraventricular pressure gradients and LVOT obstruction are likely a result of LV cavity obliteration secondary to mid- and distal-LV dyskinesia and compensatory basal hyperkinesia.[4,10] A recent case report of TC complicated by dynamic subaortic obstruction suggested that the LVOT obstruction resulted from a sigmoid septum (septal bulge) and a false tendon in the LVOT.[11] Patients with decreased LV volumes, a sigmoid septum, and a small LVOT area have a greater susceptibility to develop transient LVOT obstruction, and these patients might have an increased risk for TC in the setting of excessive sympathetic stimulation, or possibly just severe hypovolemia.[10]

Another alternative explanation suggests that the transient LV intraventricular pressure gradients might be a product of dobutamine administration.[8] In a case series of 22 patients with TC, 63% of patients (5/8) receiving dobutamine for hypotension developed LVOT obstruction with systolic anterior motion of the mitral valve, and these gradients rapidly resolved with termination of the dobutamine infusion.[8] Four of the patients treated with dobutamine also required IABP counterpulsation, and 2 of these patients (50%) had LVOT obstruction. The link between IABP use and LVOT obstruction is less clear, but IABP is likely to exacerbate the LV obstruction.

The management of TC is entirely empirical and should be based on the presentation of the patient.[6] It is imperative to recognize dynamic LV intraventricular pressure gradients and LVOT obstruction in these patients, because they require different treatment than those with hypotension from depressed LV function.[4,10,12] Similar to the approach to treating patients with HOCM, transient LVOT obstruction in TC is reduced by increasing LVOT area augmenting LVOT volume, and reducing LV ejection velocity.[10] Beta blockers and alpha-adrenceptor agonists are recommended in such patients. Beta blockers suppress LV contractility (hyperkinesia), augment diastolic filling time, increase LV end-diastolic volume (LVEDV), and increase LVOT area.[4,10,12] Phenylephrine increases afterload reducing LV intraventricular pressure gradients, augments arterial impedance, and decreases ejection velocity, which results in a larger LVEDV.[4,10,12]

While there is data that LVOT obstruction, intraventricular pressure gradients, hemodynamics, and clinical status improve following beta-adrenoceptor blockade and alpha-adrenoceptor stimulation in TC,[10] beta blockers and phenylephrine are contraindicated in the presence of large vessel vasospasm. Rather, these patients should be treated with nondihydropyridine calcium channel blockers.[4] Patients with TC without LV pressure gradients or vasospasm should be treated with beta blockers, ACE inhibitors, and aspirin, although there is minimal data supporting their use; dobutamine infusion is discouraged.[8]

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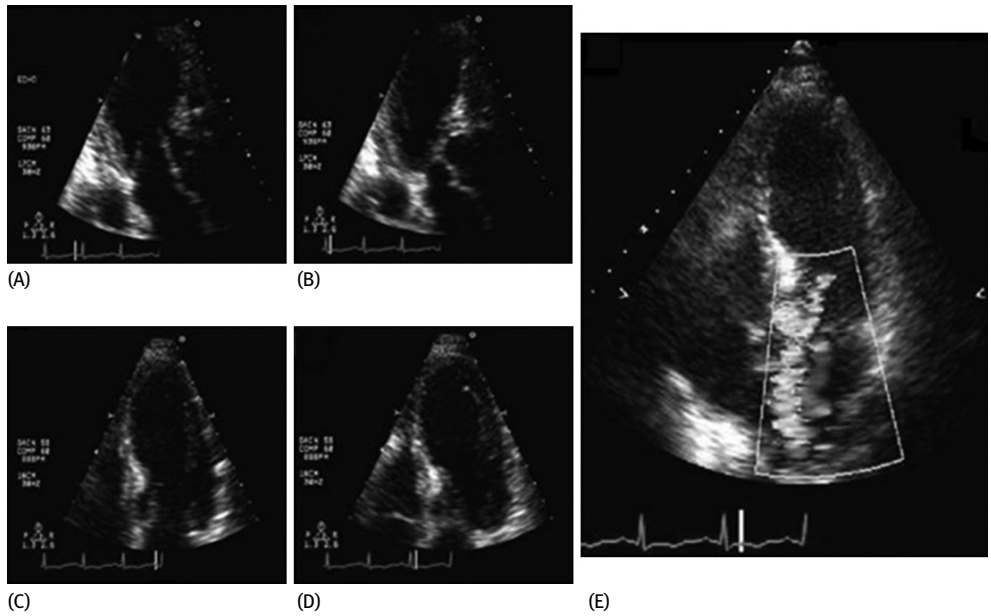

Figure 3: Two-Dimensional ECG. Apical 3-chamber of (A) diastole and (B) systole, revealing LVOT obstruction with anterior motion of the mitral valve. The apical 5-chamber view also demonstrates (C) diastole and (D) the systolic anterior motion of the mitral valve, and the (E) apical 5-chamber view of systole with color Doppler significant for severe LVOT obstruction and moderate mitral regurgitation.

In order to manage TC and its various manifestations, the pathophysiology of this syndrome must be understood more clearly. According to a recent review of 30 patients with TC, 10% had spontaneous coronary vasospasm,[13] but no patient had spontaneous large vessel spasm in the largest patient series to date, which consisted of 88 patients,[3] although coronary vasospasm could be provoked in 14 to 29% of these patients.[3,14,15] While the evidence for macrovascular abnormalities might be limited, abnormal TIMI frame counts have been reported in all three major coronary arteries, which is suggestive of microvascular impairment.[16,17] In fact, a recent study demonstrated a transient reduction in deceleration time of diastolic velocity and a transient reduction in coronary flow velocity in TC.[16]

Excessive sympathetic stimulation likely plays a central role in the development of transient LV dysfunction.[9,18–20] Physical or emotional stress preceded the development of TC in ~80% of cases.[2] These patients have significantly elevated blood levels of epine phrine, nor-epinephrine, and dopamine,[18] and TC provoked by sympathetic stimulation was not reproducible following pretreatment with alpha- and beta-adrenergic blockade in a recent rat model.[16,19] Human myocyte injury results from high concentrations of catecholamines, and cardiac sympathectomy in the Chacma baboon prevents cardiocyte injury after brain death.[10,20] Sympathetic receptor density is not uniformly distributed in the heart with the greatest density at the distal LV segment and apex providing a possible explanation for the classic LV apical ballooning seen in TC.[2,10]

Although 95% of patients with TC do not have significant obstructive CAD on coronary angiography, perfusion defects in the affected LV segments on SPECT myocardial perfusion imaging have been described.[2] In contrast to the flow-metabolism mismatch patterns seen with CAD, patients with TC have severely reduced metabolism (glucose and or fatty acid uptake) in the mid- and apical-LV regions but preserved myocardial blood flow, which suggests that metabolic abnormalities, likely due to sympathetic stimulation, contribute to the myocardial stunning in these patients.[9,21,22]

There is very little data pertaining to the role of hormones in TC, but given the predominance of postmenopausal women affected by this condition, low levels of estrogen likely lead to increased susceptibility for catecholoamine-induced myocardial stunning. In a recent model of ovariectomized rats, TC was provoked by emotional stress, and estrogen supplementation attenuated the LV abnormalities.[20] While the precise pathophysiology of TC remains unknown, the stunned myocardium is likely a product of excessive sympathetic stimulation and a combination of vascular and metabolic abnormalities.[9]

Limitations

Tako-tsubo cardiomyopathy might be linked with other forms of acute transient non-coronary neurogenic ventricular dysfunction as seen with other conditions, such as

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continued

TABLE 1: Percentage of patients with heart failure, requiring pressors and intra-aortic balloon counterpulsation, with intraventricular pressure gradients, with LVOT obstruction, and in-hospital mortality

References	n =	Patients with heart failure (%)	Patients requiring pressors (%)	Patients requiring IABP (%)	Patients with transient intraventricular pressure gradients (%)	Patients with LVOT obstruction (%)	Patients on pressors or IABP that develop LV pressure gradients or LVOT obstruction (%)	Patients in-hospital mortality (%)
Tsuchihashi et al. (3)	88	22	19	8	18	NA	NA	1
Kurisu et al. (13)	30	3	0	0	NA	NA	NA	0
Sharkey et al. (8)	22	36	36	18	18	23	63	0
Wittstein et al. (18)	19	7	NA	10	NA	NA	NA	0
Inoue et al. (23)	18	28	NA	6	NA	NA	NA	6
Bybee et al. (1)	16	44	NA	6	13	NA	NA	0
Desmet et al. (12)	13	46	NA	46	15	NA	NA	8
TOTALS	206	27	18	13	16	NA	NA	2

[a] Our literature search was completed using Pubmed by searching for case series consisting of at least 10 patients pertaining to TC, LV apical ballooning, and stress induced cardiomyopathy.
Abbreviations: CT = Tako-tsubo cardiomyopathy; IABP = intra-aortic ballon pump; LVOT = left ventricular outflow tract; NA = not applicable.

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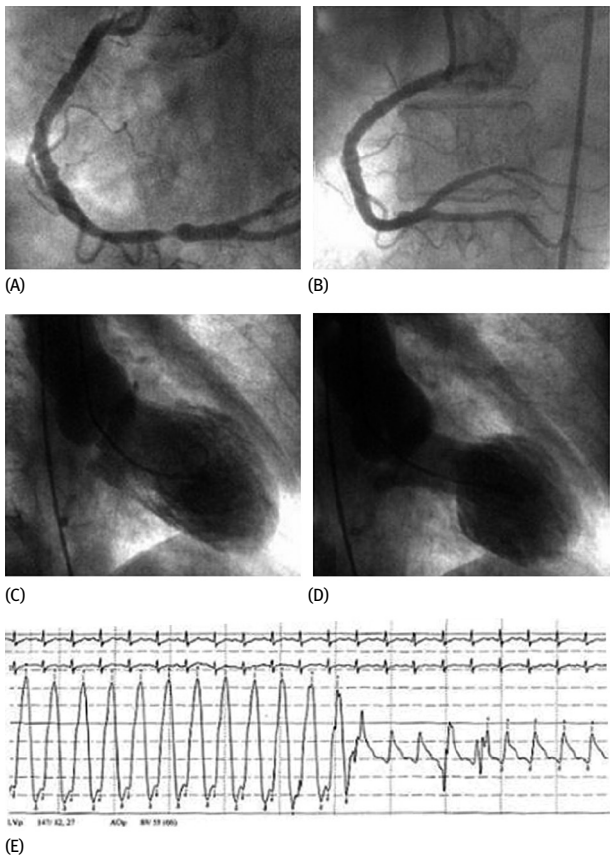

Figure 4: (A) Right coronary angiogram with a distal stenosis concerning for obstructive CAD, (B) but consistent with large vessel vasospasm. (C) Left ventriculography demonstrates end diastole and (D) the transient LV apical ballooning during systole, which is characteristic of TC. (E) Left heart catheterization pull back pressure tracings significant for a LVOT gradient of 50 mmHg.

seizures and strokes,[23,24] but using the term TC to describe all forms of transient ventricular dysfunction is controversial. Tako-tsubo cardiomyopathy initially referred to transient distal LV and apical dyskinesia, but more recently, variant forms such as myocardial dysfunction with apical sparring and mid-LV segment dyskinesia have been described.[7,25] However, some argue that these patients constitute a subset within a diverse disease spectrum and suggest that the term TC is inferior to using the term stress cardiomyopathy, as one might confuse mid-ventricular ballooning with apical ballooning.[25] Although a consistent nomenclature must be addressed and implemented, the underlying pathophysiology and clinical significance of this diverse phenotype is likely the same.[25]

Conclusion

There is mounting evidence that excessive sympathetic stimulation and resultant metabolic and vascular abnormalities account for the myocardial dysfunction of mid-to distal-LV segments in patients who present with TC. While TC is usually benign, this reversible syndrome can present with severe abnormalities such as LVOT obstruction and cardiogenic shock. It is imperative that clinicians understand the pathophysiology behind TC, become more cognizant of its myriad of manifestations, and adjust their management accordingly.

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