Chapter 8
Takotsubo Cardiomyopathy – An Interesting and Somewhat Unexplained Clinical Entity

Eduardo D. Gabe and John A. Ambrose

Abstract Takotsubo cardiomyopathy is a curious, underreported syndrome of transient left ventricular dysfunction unrelated to coronary artery disease, often presenting as an ACS in postmenopausal women usually following a significant mental or physical stress. Since its initial description nearly 25 years ago, it has been reported under various scenarios. While criteria for diagnosis have been proposed, there remain several unresolved issues pertaining to its incidence, pathophysiology and treatment. This chapters reviews these unresolved issues.

Keywords Takotsubo • "Broken Heart" syndrome

Introduction

Takotsubo cardiomyopathy (TCM) is a curious clinical entity characterized by transient left ventricular dysfunction usually involving the antero apical and infero apical regions of the myocardium in the absence of significant coronary artery disease (Fig. 8.1). The syndrome often presents with chest pain and/or dyspnea, dynamic reversible ST-T segment abnormalities, and mildly increased cardiac enzymes disproportionate to the extent of wall motion abnormalities. Most patients are usually elderly women and there is often a significant mental or physical stress preceding the appearance of symptoms. Common triggers that have been identified which include the death of a loved one, becoming a victim of theft, the experience of a great loss such as with gambling, a surprise party or severe illness (hospitalization in an intensive care unit), etc. [1]. In others, an acute neurologic event, most commonly a subarachnoid hemorrhage is the precipitating event. While elevated catecholamine

E.D. Gabe, MD, PhD, FACC (✉)
Department of Cardiology, Otamendi Hospital, Buenos Aires, Argentina
e-mail: edudagabe@gmail.com

J.A. Ambrose, MD
Chief of Cardiology, UCSF Fresno, Fresno, CA, USA

Department of Medicine, UCSF Community Regional Medical Center, Fresno, CA, USA

J.A. Ambrose, A.E. Rodríguez (eds.), *Controversies in Cardiology*,
DOI 10.1007/978-3-319-20415-4_8

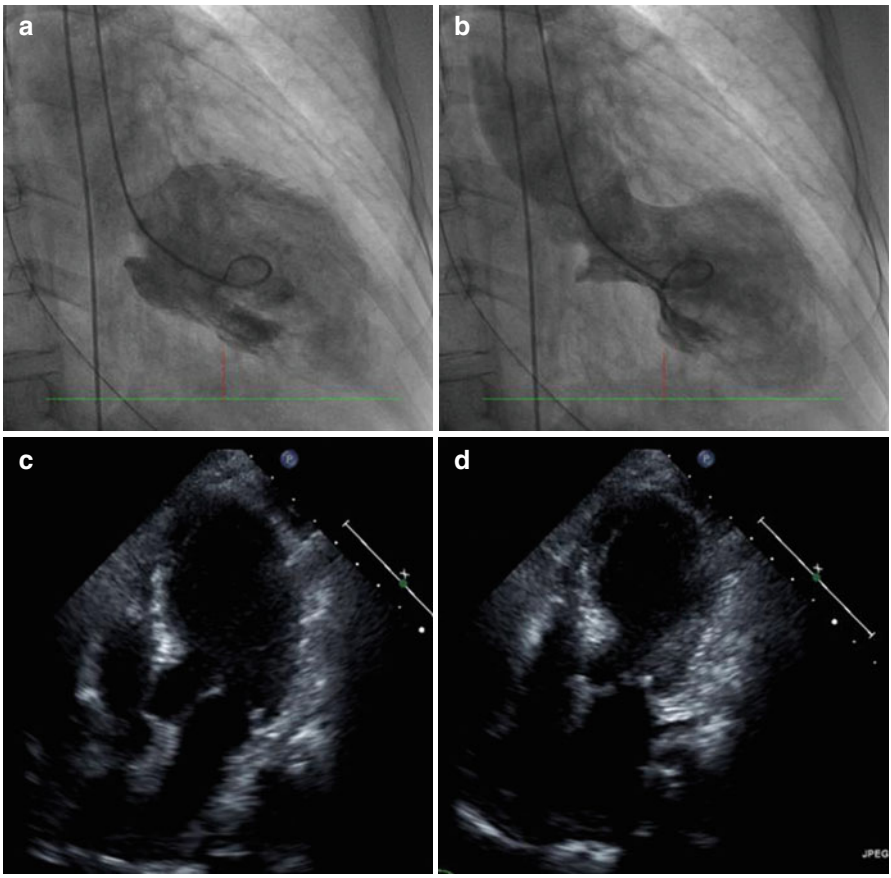

Fig. 8.1 The typical end diastolic (**a**) and end systolic (**c**) left ventricular angiographic frames from a 72 year old female who presented with an ACS after the death of her sister. Similar findings are also seen on a four chamber echocardiogram-End diastole (**b**) and end systole (**d**)

levels have been suggested as a significant pathophysiologic mechanism in most patients, in others, the pathophysiology is unknown as well as how elevated catecholamines alter left ventricular function. Since it was first described in 1991, multiple articles have been published on this subject. However, several aspects of the disease remain unresolved. These revolve around its incidence, pathophysiology, the diagnostic criteria used to define it and its appropriate management [2–5].

Incidence

Since it was first recognized, it has been reported in most studies that about 1–2 % of patients diagnosed as an ACS could suffer from TCM. However, its true incidence is largely unknown. Possible reasons that contribute to this include the fact that there is often a low index of clinical suspicion for TCM and TCM can often

masquerade as other syndromes. While diagnostic criteria have been proposed, these criteria are very specific although probably relatively insensitive leading to under diagnosis. Since the presence of severe coronary artery disease is an exclusion according to the Mayo criteria, a typical presentation in an elderly female may be misdiagnosed as related to coronary disease [6]. The prevalence estimate of TCM comes from small series of consecutive patients with suspected ACS [7–10]. While each of these series included a small number of patients with TCM, they represented approximately 1.7–2.2 % of the cases admitted to the coronary care unit with suspected ACS. In a preliminary investigation, researchers at the University of Arkansas identified 21,748 patients diagnosed with TCM in 2011 using a database of national hospital discharge in the USA [11]. In an analysis of cases by state, it was observed that Vermont and Missouri had the highest rate, with 380 per million population in Vermont and 169 per million in Missouri. The rate of patients with TCM in Vermont in 2011 was more than double that in the other states. This was the same year that Tropical Storm Irene hit the state with heavy rains and wind. Similarly, the researchers found a rate of 169 cases per million in Missouri in 2011, the same year that a massive tornado devastated Joplin, Mo. Most states had fewer than 150 cases per million inhabitants [11].

There are other data suggesting that the incidence may be more common than previously published particularly if one examines post menopausal women presenting with ACS. Sy et al. prospectively evaluated 1297 consecutive postmenopausal women with a positive troponin, 323 (24.9 %) of whom met criteria for acute myocardial infarction according to the Universal Definition. Of these, 19 (5.9 %) met criteria for definite or probable TCM [12]. We also believe that TCM can pose as other syndromes previously reported in the literature. Other than the cerebral T waves associated with subarachnoid hemorrhage, LV dysfunction associated with sepsis [13], the occasional patient with normal appearing coronary arteries on angiography after thrombolytic therapy and viral myocarditis masquerading as acute myocardial infarction may represent, in many cases, TCM. In the later report, most patients were elderly women with transient LV dysfunction and no coronary obstruction [14]. Their biopsies were not inconsistent with that seen in TCM.

Pathophysiology

Several theories have been proposed to explain the pathophysiology of TCM. These include catecholamine excess, multiple epicardial coronary artery spasm, microvascular dysfunction and acute outflow tract obstruction in the presence of low estrogen levels. These theories are not mutually exclusive.

In general, the LV dysfunction of TCM whether it is the apical variant or the other less frequent presentations (mid ventricular or basal) does not correspond to a single coronary artery territory. In the usual apical variant, the akinesis is more extensive than the territory supplied by the left anterior descending artery. While Migliore et al. [15] found that myocardial bridging of the left anterior descending on angiography or CT imaging was a common finding in patients with TCM, it is highly unlikely that this is causative. Likewise, Ibanez et al. suggested that TCM

could be an aborted myocardial infarction with spontaneous lysis of the thrombus [16]. Again, the overall evidence is not supportive.

What has been suggested is that reversible dysfunction of the coronary microcirculation might be an important pathophysiologic mechanism. Utilizing myocardial contrast echocardiography and infusions of adenosine, Galiuto et al. showed that adenosine transiently improved microvascular perfusion and wall motion in TCM but not in acute anterior STEMI [17]. The cause of this intense microvascular constriction and the predilection for this region of the myocardium is still largely unknown, although the effect of sympathetic stimulation on the vasculature is probably an important mechanism. Supraphysiologic levels of catecholamines have been described in most but not all patients with TCM and it has been suggested that this leads to myocardial stunning. Catecholamine and dopamine plasma levels during the acute presentation of TCM are significantly higher than those found in individuals with acute myocardial infarction and Killip class III/IV and remain very high even a week after the onset of symptoms [18]. Cardiac biopsy specimens when performed acutely in some patients with TCM have shown monocyte infiltration and contraction band necrosis consistent with catecholamine excess [18]. Excessive catecholamine release might generate microvascular spasm and endothelial dysfunction leading to myocardial stunning [19–21]. Transient LV dysfunction similar to TCM could be induced in rats exposed to physical stress with elevated levels of catecholamines [22]. It has also been suggested that increased catecholamines generate increases in reactive oxygen species that directly injure vascular cells and cardiac myocytes [18].

Why is the apex of the left ventricle usually involved in TCM? Ballooning of the apical region might be related to the predominance of sympathetic receptor density in the apical portion of the left ventricle. 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 TCM. High levels of catecholamines may be negatively ionotropic when the β1 receptor is over stimulated leading to transient myocardial stunning [23]. Supporting this hypothesis is the high frequency of antecedent mental or physical stress and the similarity of the wall motion abnormalities in TCM to those with the cardiomyopathy of pheochromocytoma or catecholamine excess [24, 25]. Unfortunately, elevated catecholamine levels have not been found in all patients with TCM.

Another hypothesis that has been proposed is multivessel spasm of epicardial coronary arteries. It seems unlikely that the left ventricular dysfunction occurring in this syndrome could be due only to spasm of a single coronary artery as mentioned above. No conclusive evidence of multivessel spasm has been found to explain most cases of TCM, although it is suggested that transient spasm might explain a minority particularly in Japan. In a study in which spasm was evaluated, multivessel spasm was demonstrated in a few patients [2]. However, persistent ST elevation without coronary stenosis on angiography could not be related to epicardial spasm as the primary pathophysiology of TCM [2].

Another possibility regarding the pathophysiology of TCM has been the demonstration of acute outflow tract obstruction in some patients with TCM [20].

Hypercontractility of the basal segments in the usual apical variant may lead to outflow tract obstruction in the small left ventricles of postmenopausal women. The acute pressure overload at the thinned out apex related to obstruction could lead to transient apical akinesis. However, if this mechanism is causative, it is involved in only the minority of cases.

Metabolic abnormalities have also been described in TCM, including a reduction in fatty acid metabolism similar to what occurs under conditions of ischemia. This has been documented through SPECT imaging with I-123 BMIPP [26]. On PET imaging, reduced perfusion with N-13 ammonia and decreased metabolism with F-18 FDG imaging have also been described. The radio-iodinated analog for norepinephrine, I-123 MIBG has also been used to demonstrate a suppression of myocardial sympathetic nerve function in response to myocardial ischemia in TCM. These findings of transient decreased perfusion with reduction in metabolism and sympathetic nerve function are characteristic of myocardial stunning. These findings are likely secondary to TCM rather than primary mechanisms.

All authors agree that the vast majority of patients (typically ≥90 %) diagnosed with TCM are postmenopausal women. How does estrogen and specifically the estrogen deficiency following menopause contribute to TCM? The answer is not clear. There could be a complex interaction between neuro-hormonal factors, the genetic profile, anatomical abnormalities and other factors that jointly contribute to the cardiac dysfunction. Stress-mediated vasoconstriction may be enhanced in the presence of estrogen deficiency [27]. Estrogen deficiency promotes vasomotor instability prone to vasoconstriction, endothelial dysfunction and thus microvascular dysfunction. Lower estrogen levels may explain the gender disparity in the expression of this cardiac entity [27–29].

In summary, there are probably multiple interrelated pathophysiologic mechanisms in TCM. Most revolve around the effects of a transient increase in catecholamine levels in the presence of estrogen deficiency. Transient left ventricular dysfunction results, possibly related to catecholamine effects on β receptors upregulated at the apex and transient microvascular dysfunction. In a few patients, basal hypercontractility leads to outflow tract obstruction or multi vessel epicardial spasm is present. Both of these later conditions might be causative of TCM or just epi phenomena. Of course, these mechanisms might not apply to the occasional man or younger woman with TCM. One wonders whether or not there is a genetic component that predisposes some individuals to this condition. We believe that the molecular mechanisms underlying this syndrome also require further study.

Making the Diagnosis of TCM

Diagnostic criteria have been proposed by various authors (Tables 8.1, 8.2, 8.3, and 8.4) [30–33]. The Mayo Clinic (Table 8.5) [34, 35] criteria are the most widely accepted. Most criteria exclude patients with head trauma, intracranial or subarachnoid hemorrhage which does not seem logical since these patients often develop the typical signs of TCM on ECG and non invasive imaging. Significant epicardial

Table 8.1 Abe and Kondo criteria

Major criteria:
Reversible left ventricular ballooning with abnormalities of apical motility and hypercontractility of the basal segments.
Abnormalities of the ST segment/T wave on the ECG, simulating acute myocardial infarction.
Minor criteria:
Physical or emotional stress as triggering factors.
Limited elevation of the cardiac enzymes.
Precordial pain.
Exclusion criteria:
Ischaemic myocardial stunning.
Subarachnoid haemorrhage.
Pheochromocytoma crisis.
Acute myocarditis.
Tachycardia-induced cardiomyopathy.

Table 8.2 Prasad criteria

Transient hypokinesia, akinesia, or dyskinesia of the middle segments of the LV, with or without alterations at the apex.
Regional abnormalities of wall motility extend beyond the area of distribution of a single epicardial vessel.
Absence of an obstructed coronary artery or angiographic evidence of acute rupture of a plaque.
New ECG abnormalities (ST elevation and/or T-wave inversion) or elevation of cardiac troponin.
Absence of:
Recent head injury
Intracranial haemorrhage
Pheochromocytoma
Myocarditis
Hypertrophic cardiomyopathy

coronary artery disease is a natural exclusion although, as mentioned earlier, this probably leads to under diagnosis since TCM is not ordinarily diagnosed in the presence of severe CAD even when the acute signs are otherwise classic and the recovery of function is typical. Given the advanced age of most patients, concomitant coronary artery disease probably excludes many potential patients. Other situations may also preclude diagnosis such as not performing an angiogram to exclude CAD because the patient is too sick, i.e. ICU patients with trauma or sepsis etc. Occasionally, potential patients die before a diagnosis can be confirmed by a repeat imaging study showing improvement in regional wall motion.

After initial reports of TCM as the typical apical left ventricular dysfunction, new variants of altered ventricular geometry were reported. The dysfunction can preserve the apex and affect different segments of the left ventricle and right ventricle as well. Akinesia of the middle ventricular segment with normal or increased apical and basal contraction is termed the mid ventricular variant. Basal akinesia

Table 8.3 Segovia Cubero criteria

Previous conditions (**both obligatory**):
1. Evidence of a transient apical dysfunction of the LV with the typical form in systole (rounded apex with narrow neck due to hypercontractility of the basal segments), diagnosed by angiography, echocardiography, isotope scans, or cardiac magnetic resonance imaging. The disturbance typically reverts in 2–3 weeks, although it can persist for up to 2 months.
2. Absence of other conditions associated with regional transient systolic dysfunction of the LV: subarachnoid hemorrhage, pheochromocytoma, ischemic myocardial stunning, drugs (cocaine), myocarditis, etc.
Diagnostic criteria:
1. Major: Early coronary angiography (within the first 24 h) showing no anatomical lesions.
2. Minor:
Early coronary angiography showing non-significant lesions (less than 50 % without characteristics of a complicated plaque or intraluminal thrombus).
Late coronary angiography (from the second to the seventh day after the onset of the syndrome) showing no significant lesions.
Physical or psychological stress as the trigger of the disorder.
Typical ECG changes:
ST segment elevation in the acute phase, more marked in V4–V6 than in V1–V3.
Appearance of Q waves that disappear after the acute phase.
Very prominent negative T waves in V1–V6.
QTc prolongation.
Woman over 50 years of age.
Confirmed TADS: 1 major criterion or 2 or more minor criteria, including an angiographic criterion.
Probable TADS: 2 or more minor criteria, with no angiographic criterion.
TADS: transient apical dysfunction syndrome.

with preserved apical contractility is referred to as "inverted Takotsubo". The typical apical variant is observed in over 2/3 s of patients [8, 36].

Eitel et al. [37] have examined the role of MRI in 59 patients with clinical manifestations of TCM (patients with an ACS without significant obstructive coronary disease and characteristic wall motion abnormalities). Based on magnetic resonance imaging only, a diagnosis of MCT was established in 68 % of patients. Typically, there is no late enhancement of gadolinium with TCM in comparison to LV dysfunction related to infarction. Presumably, this technique might be used in some patients with CAD and otherwise a typical TCM presentation to suggest the diagnosis.

Acute and Chronic Management of TCM

There is no specific treatment and the same supportive therapy used in any cardiomyopathy is employed. The optimal treatment has not been established. Most would use beta blockers given the presumed role of excessive catecholamines but it is

Table 8.4 Kawai criteria

Exclusion criteria:
1. Significant organic stenosis or spasm of a coronary artery. In particular, AMI due to a lesion of the anterior descending artery of the left coronary artery, which irrigates a large territory including the apex of the LV (urgent coronary angiography is desirable in order to view the image in the acute phase; during the chronic phase, coronary angiography is necessary to confirm the presence or absence of significant stenotic lesions or abnormal lesions that could explain the ventricular contraction).
2. Cerebrovascular disturbances.
3. Pheochromocytoma.
4. Viral or idiopathic myocarditis.
(Note: Coronary angiography is required for the exclusion of coronary artery lesions. Takotsubo-like myocardial dysfunction can occur in conditions such as cerebrovascular disorders or phaeochromocytoma).
Diagnostic references:
1. Symptoms: Precordial pain and dyspnoea similar to the findings in the acute coronary syndrome. Takotsubo cardiomyopathy can also occur without symptoms.
2. Triggers: Emotional or physical stress, although it can also occur without any obvious trigger.
3. Age and gender: There is a recognized tendency to a higher frequency in elderly individuals, principally women.
4. Ventricular morphology: Apical ballooning with rapid recovery on ventriculography and echocardiography.
5. ECG: ST elevation may be observed immediately after the event. T waves progressively become negative in various leads and the QT interval progressively lengthens. These changes gradually improve, but the T waves may remain negative for months. Pathological Q waves and alterations of the QRS voltage may be observed in the acute phase.
6. Cardiac biomarkers: There is only a slight rise in the cardiac enzymes and troponin.
7. Nuclear medicine scan of the heart: Abnormalities may be detected on myocardial gamma scan in some cases.
8. Prognosis: Recovery is rapid in most cases, but some patients develop acute pulmonary edema and other sequelae, even death.

Table 8.5 Diagnostic criteria of the Mayo Clinic

Suspicion of AMI based on precordial pain and ST elevation observed on the acute-phase ECG.
Transient hypokinesia or akinesia of the middle and apical regions of the LV and functional hyperkinesia of the basal region, observed on ventriculography or echocardiography.
Normal coronary arteries confirmed by arteriography (luminal narrowing of less than 50 % in all the coronary arteries) in the first 24 h after the onset of symptoms.
Absence of recent significant head injury, intracranial hemorrhage, suspicion of pheochromocytoma, myocarditis, or hypertrophic cardiomyopathy

unknown whether these hasten recovery. Furthermore, it is unclear whether selective beta blockers such as metoprolol (a selective β1 blocker) versus carvedilol (both a non selective β and α blocker) are the preferred agent. While most would continue beta blockers chronically, there are also no data supporting the fact that these agents reduce recurrences. Fortunately, the recurrence rate is $\leq$10 %.

If there is adequate blood pressure, medical therapy usually includes not only a beta-blocker but also an angiotensin converting enzyme inhibitor, or angiotensin II receptor blocker. Systemic anticoagulation should be considered if a left ventricular thrombus is identified or the wall motion abnormalities are slow to recover. Inotropic support may be necessary if the blood pressure is low but should not be used in patients with outflow tract obstruction. Thus, this indicates the importance of a complete echocardiographic study or hemodynamic measurements at the time of angiography. A definitive diagnosis of TCM requires that the coronary arteries are visualized and are normal or non obstructive. An intra-aortic balloon pump or other methods of circulatory support is indicated with marked left ventricular dysfunction associated with severe hypotension or shock in the absence of outflow tract obstruction. Hospital mortality in most of the published series is <3 %. These patients should also be monitored carefully after admission to prevent significant arrhythmias.

If an elderly female is admitted with a STEMI- like presentation particularly involving the anterior wall and is not at or near a hospital with primary PCI capability, should she receive thrombolytic therapy? One must always individualize therapy but, unless she is at high risk of bleeding, the answer is yes as the therapy could be life saving. However, angiography is always preferable to exclude the occasional TCM and provide the appropriate interventional therapy. This is particularly suggested if the index of suspicion for TCM is high such as when there is a preceding great emotional stress and a large apical wall motion abnormality is seen on echocardiography or angiography.

Conclusion

In spite of being a reversible, mostly benign form of cardiomyopathy, there must always be a high index of suspicion for this diagnosis particularly in post menopausal women presenting with an ACS or unexplained LV dysfunction. Although there are controversial data regarding the incidence, pathophysiologic mechanisms, diagnostic criteria, therapeutic strategies and perhaps even the name of the syndrome, always consider TCM as a possibility particularly in this population. You might be surprised how often you will find it!

References

1. Sharkey SW, Lesser JR, Zenovich AG, et al. Acute and reversible cardiomyopathy provoked by stress in women from the United States. Circulation. 2005;111:472–9.
2. Tsuchihashi K, Ueshima K, Uchida T, et al. Transient left ventricular apical ballooning without coronary artery stenosis: a novel heart syndrome mimicking acute myocardial infarction: Angina Pectoris–Myocardial Infarction Investigations in Japan. J Am Coll Cardiol. 2001;38:11–8.

3. Kurisu S, Sato H, Kawagoe T, et al. Tako-tsubo-like left ventricular dysfunction with ST-segment elevation: a novel cardiac syndrome mimicking acute myocardial infarction. Am Heart J. 2002;143:448–55.
4. Akashi YJ, Musha H, Kida K, et al. Reversible ventricular dysfunction takotsubo cardiomyopathy. Eur J Heart Fail. 2005;7:1171–6.
5. Eitel I, von Knobelsdorff-Brenkenhoff F, Bernhardt P, et al. Clinical characteristics and cardiovascular magnetic resonance findings in stress (takotsubo) cardiomyopathy. JAMA. 2011;306:277–86.
6. Gaibazzi N, Ugo F, Vignali L, Zoni A, Reverberi C, Gherli T. Tako-Tsubo cardiomyopathy with coronary artery stenosis: a case-series challenging the original definition. Int J Cardiol. 2009;133:205–12.
7. Akashi YJ, Goldstein DS, Goldstein DS, Barbaro G, Ueyama T. Takotsubo cardiomyopathy: a new form of acute, reversible heart failure. Circulation. 2008;118:2754–62.
8. Kurowski V, Kaiser A, von Hof K, et al. Apical and midventricular transient left ventricular dysfunction syndrome (tako-tsubo cardiomyopathy): frequency, mechanisms, and prognosis. Chest. 2007;132:809–16.
9. Bybee KA, Kara T, Prasad A, et al. Transient left ventricular apical ballooning syndrome: a mimic of ST-segment elevation myocardial infarction. Ann Intern Med. 2004;141:858–65.
10. Gianni M, Dentali F, Grandi AM, et al. Apical ballooning syndrome or takotsubo cardiomyopathy: a systematic review. Eur Heart J. 2006;27:1523–9.
11. Pant S, Deshmukh A, Mehta K, et al. Clustering of takotsubo cardiomyopathy cases in United States in 2011. J Am Coll Cardiol. 2014;63(12):A828.
12. Sy F, Basroan J, Zheng H, et al. Frequency of takotsubo cardiomyopathy in postmenopausal women presenting with an acute coronary syndrome. Am J Cardiol. 2013;112:479–82.
13. Cunnion RE, Parrillo JE. Myocardial dysfunction in sepsis: recent insights. Chest. 1989;95:941–5.
14. Narula J, Khaw BA, Dec GW, et al. Brief report: recognition of acute myocarditis masquerading as acute myocardial infarction. N Engl J Med. 1993;328:100–4.
15. Migliore F, Maffei E, Perazzolo MM, et al. LAD coronary artery myocardial bridging and apical ballooning syndrome. JACC Cardiovasc Imaging. 2013;6(1):32–41.
16. Ibanez B, Navarro F, Cordoba M, Alberca PM, Farre J. Tako-tsubo transient left ventricular apical ballooning: is intravascular ultrasound the key to resolve the enigma? Heart. 2005;91:102–4.
17. Galiuto L, De Caterina AR, Porfidia A, et al. Reversible coronary microvascular dysfunction: a common pathogenetic mechanism in apical ballooning or Tako-Tsubo syndrome. Eur Heart J. 2010;31:1319–27.
18. Wittstein IS, Thiemann DR, Lima JA, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. N Engl J Med. 2005;352(6):539–48.
19. Bielecka-Dabrowa A, Mikhailidis DP, Hannam S, et al. Takotsubo cardiomyopathy-the current state of knowledge. Int J Cardiol. 2010;142:120–5.
20. Merli E, Sutcliffe S, Gori M, Sutherland GG. Tako-Tsubo cardiomyopathy: new insights into the possible underlying pathophysiology. Eur J Echocardiogr. 2006;7:53–61.
21. Goldstein DS, Eisenhofer G, Kopin IJ. Sources and significance of plasma levels of catechols and their metabolites in humans. J Pharmacol Exp Ther. 2003;305:800–11.
22. Ueyama T, Kawabe T, Hano T, et al. Upregulation of heme oxygenase-1 in an animal model of Takotsubo cardiomyopathy. Circ J. 2009;73:1141–6.
23. Lyon AR, Rees PSC, Prasad S, Poole-Wilson PA, Harding SE. Stress (Takotsubo) cardiomyopathy—a novel pathophysiological hypothesis to explain catecholamine-induced acute myocardial stunning. Nat Clin Pract Cardiovasc Med. 2008;5, E2. doi:10.1038/ncpcardio1236.
24. Shaw T, Rafferty P, Tait GW. Transient shock and myocardial impairment caused by phaeochromocytoma crisis. Br Heart J. 1987;57:194–8.
25. Yamanaka O, Fujiwara Y, Takamura T, et al. 'Myocardial stunning'-like phenomenon during a crisis of pheochromocytoma. Jpn Circ J. 1994;58:737–42.

26. Alexanderson E, Cruz P, Talayero JA, Damas F, Zeron J, Meave A. Transient perfusion and motion abnormalities in takotsubo cardiomyopathy. J Nucl Cardiol. 2007;14(1):129–33.
27. Kaski JC. Cardiac syndrome X in women: the role of oestrogen deficiency. Heart. 2006;92 Suppl 3:iii5–9.
28. Johnson BD, Shaw LJ, Buchthal SD, et al. Prognosis in women with myocardial ischemia in the absence of obstructive coronary disease: results from the National Institutes of Health-National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE). Circulation. 2004;109:2993–9.
29. Demir H, Kahraman G, Isgoren S, et al. Evaluation of post-stress left ventricular dysfunction and its relationship with perfusion abnormalities using gated SPECT in patients with cardiac syndrome X. Nucl Med Commun. 2008;29:208–14.
30. Abe Y, Kondo M, Matsuoka R, et al. Assessment of clinical features in transient left ventricular apical ballooning. J Am Coll Cardiol. 2003;41:737–42.
31. Prasad A. Apical ballooning syndrome. An important differential diagnosis of acute myocardial infarction. Circulation. 2007;115:e56–9.
32. Segovia Cubero J, Peraira Moral R. Transient apical ballooning syndrome: a transition towards adulthood. Rev Esp Cardiol. 2004;57:194–7 [in Spanish with English abstract].
33. Kawai S, Kitabatake A, Tomoike H, et al. Guidelines for diagnosis of takotsubo (ampulla) cardiomyopathy. Circ J. 2007;71:990–2.
34. Prasad A, Lerman A, Rihal CS. Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction. Am Heart J. 2008;155:408–17.
35. Madhavan M, Prasad A. Proposed Mayo Clinic criteria for the diagnosis of Tako-Tsubo cardiomyopathy and long-term prognosis. Herz. 2010;35(4):240–3. doi:10.1007/s00059-010-3339-x.
36. Cortese B, Robotti S, Puggioni E, et al. Transient left ventricular apical ballooning syndrome: all that glitters is not apical. J Cardiovasc Med (Hagerstown). 2007;8:934–6.
37. Eitel I, Behrendt F, Schindler K, Kivelitz D, Gutberlet M, Schuler G, et al. Differential diagnosis of suspected apical ballooning syndrome using contrast-enhanced magnetic resonance imaging. Eur Heart J. 2008;29:2651–9.