Review Article

Takotsubo Cardiomyopathy: A Literature Review

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Abstract

Takotsubo cardiomyopathy (TC) is a transient non-ischemic cardiomyopathy, whose frequency has increased rapidly over the past few years. It is characterized by regional left ventricular wall motion abnormality, with a circumferential pattern that spreads beyond a coronary artery supply territory. It can resolve with an almost complete restoration of ventricular function within days to months. TC is more prevalent among postmenopausal women, and less prevalent in Hispanics and African-Americans. It is a heterogeneous syndrome, and several etiologies have been proposed for its pathogenesis. The central hypothesis is supported by catecholamine excess and hyperactivity of the nervous system. The clinical presentation usually overlaps with the presentation of acute coronary syndrome (ACS) which calls for an early diagnosis. In light of this, several laboratory, electrocardiographic and imaging findings have been studied in order to form the clinical diagnosis of Takotsubo Cardiomyopathy.

INTRODUCTION AND BACKGROUND

Takotsubo cardiomyopathy (TC) is transient non-ischemic cardiomyopathy described initially by Sato et al. in 1990 [1]. It is characterized by hypokinetic or akinetic apical or midventricular myocardium, and symptoms of chest pain and shortness of breath after acute mental or physical stress [2]. It is anticipated that TC accounts for nearly 1–2% of all patients with suspected acute coronary syndrome (ACS) and most commonly affects middle-aged and older women [3]. Patients are typically Asian or Caucasian [4]. The frequency of the diagnosis of TC has increased over the past few years, in fact, the incidence of TC hospitalization has increased with a 3-fold increase in the United States between 2007 and 2012 [5]. In the early phase TC mimics ACS, leading to almost universal use of cardiac catheterization.

The exact prevalence is unknown, as the syndrome may be under-diagnosed. However, women are nine times more predisposed than men to the disease. Furthermore, postmenopausal women (women over 55 years of age) have a five times higher risk than women under 55 years of age [6]. In Japan, TC is more prevalent among men, for unclear reasons [7]. To date, TC has been reported in multiple races, but it has been uncommon in Hispanics and African-Americans [8]. Chronic comorbidities including malignancy tend to predispose towards the development of TC [9]. The acute prognosis is now known to be worse than what was initially thought. Moreover, according to the SWEDEHEART study, the early and late mortality of TC is similar to that of ACS [10].

REVIEW

The hallmark of takotsubo cardiomyopathy is regional left ventricular wall motion abnormality, with a circumferential pattern that spreads beyond a coronary artery supply territory. It can resolve with an almost complete restoration of ventricular function within days to months [2,4,9]. The ventricular wall motion abnormality may affect the apical, mid-apical, mid-ventricular, mid-basal, or basal segments of the left ventricle [6]. TC predominantly affects the left ventricle. However, right ventricular involvement has been reported in approximately one-third of the patients [11]. The classic form (apical ballooning), has significant reversible mitral regurgitation (MR) coupled with high brain natriuretic peptide (BNP) levels. Conversely, the inverted (basal) form seems to have lower levels of BNP as well as a low incidence of MR but a high level of troponins [12].

TC is a heterogeneous syndrome, and several etiologies have been proposed. The main proposed mechanisms are catecholamine excess, derangement of myocardial glucose and fatty acid metabolism, microcirculatory dysfunction, coronary vasospasm, and estrogen deficiency. None of these pathophysiological theories has been shown to be definitive, suggesting that all of them may be involved to some extent.

Increased epinephrine levels could trigger a switch of B2 adrenoreceptor (B2AR) from Gs (stimulatory) to Gi (inhibitory) protein signaling. This change in receptor signaling is negatively inotropic. The apical myocardium might be more susceptible to this effect leading to apical stunning [13]. Blood-borne catecholamine myocardial toxicity has also been proposed as one of the pathophysiological mechanisms of TC. This is based on the similarity of histological changes in the myocardium in patients with pheochromocytoma [2]. Hyperactivation of the sympathetic nervous system ($\alpha 1$ and $\beta 1$) by norepinephrine may also cause coronary vasospasm and hyperdynamic basal myocardial contractions [14]. Furthermore, reports of abnormalities in Positron Emission Tomography (PET) studies may also suggest defects in myocardial glucose and fatty acid metabolism in Takotsubo syndrome [15].

The clinical picture of TC coincides with that of ACS (with or without ST elevation). These conditions can be differentiated by coronary angiography, which would demonstrate obstructive coronary artery disease in the vessel supplying the dysfunctional ventricular territory in ACS. Of note, some patients have concurrent ACS and stress cardiomyopathy [16, 17].

Additional differential diagnoses include myocarditis, pheochromocytoma, cocaine-related ACS, amphetamine abuse, peripartum cardiomyopathy and cerebrovascular disease. Aortic dissection and pulmonary embolism should be kept under consideration as well.

The Modified Mayo Clinic diagnostic criteria helps to differentiate TC from its major differential diagnoses [18,19]. All four of the following criteria must be met for diagnosing TC: 1) Transient left ventricular (LV) systolic dysfunction (hypokinesis, akinesis, or dyskinesis); 2) Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture; 3) New electrocardiographic abnormalities (either ST-segment elevation and/or T wave inversion) or modest elevation in cardiac troponin; and 4) The absolute absence of pheochromocytoma or myocarditis. The criteria are designed to be clinically applied at the time of admission.

Investigations including lab tests for catecholamine levels, cardiac biomarkers, lipid levels and markers such as soluble lectin like oxidized LDL receptor-1 (sLOX-1), Copeptin, ischemic modified albumin (IMA), soluble suppression of tumorigenicity-2 (sST2), etc. can be useful to differentiate TC from other diseases. Imaging modalities including echocardiogram, CT angiography, invasive coronary angiogram, cardiac MRI, single photon emission computed tomography (SPECT), PET scans and ECG findings have been proposed as well.

TC is associated with increased serum cardiac biomarkers of myonecrosis (troponin I and T, creatine kinase and myoglobin). Cardiac troponin levels are elevated in most cases of TC because of their higher sensitivity [6,20]. Several investigational markers including Copeptin [21], lipid profile [22], sLOX-1 [23], IMA [24], sST-2 [25] can also be deranged and should be checked during the evaluation of a suspected TC. Elevated sLOX-1 has been found to be comparable to troponin elevations, and changes in the level of sST2 have additional predictive value for patients of TC with a normal Troponin I [23]. Hyperalphalipoproteinemia (HDL-C) and hypotriglyceridemia (LDL-C and triglycerides) have also been reported in 40% cases [22].

The Natriuretic family of peptide hormones has natriuretic properties, vasodilatory properties and pleiotropic effects [26]. NPs include: Atrial natriuretic peptide (ANP), BNP and C-type natriuretic peptide (CNP), which are intimately involved in cardio-renal homeostasis. ANP is synthesized mainly in atria, BNP is released primarily from ventricles, whereas nervous tissue and vascular endothelium mainly produce CNP [27, 28].

NPs effects in target tissues are mediated by soluble guanylyl cyclase (GC) receptors. NPR-A, NPR-B, and NPR-C are the natriuretic peptide receptors [26, 27]. ANP and BNP act primarily through NPR-A and cause inhibition of aldosterone synthesis, block of vasopressin and adrenocorticotropic hormone release, and sympatholysis. They also contribute to modulate natriuresis, vasodilation, thirst suppression [26, 29]. CNP is less natriuretic and acts primarily via NPR-B. This causes vascular tone modulation, cardiac remodeling, vascular smooth muscle proliferation. NPR-C plays an essential role in NPs clearance and mediates vasoprotective properties of CNP [20, 27, 30].

BNP and N-terminal pro-BNP (an inactive by-product of BNP formation) have been widely studied due to their vital role in the diagnosis, and treatment of heart failure [31]. BNP is initially produced as preproBNP which is successively cleaved to obtain a biologically active α-carboxy terminal peptide along with the amino-terminal end. The plasma half-life of NT-proBNP is longer (120 min) and it is cleared renally. However, BNP has a comparatively shorter half-life (about 20 min) and is cleared by NPR-C and neutral endopeptidase (Neprilysin) [32].

BNP and NT-proBNP are elevated in some patients with heart failure, ACS, valvular heart disease, pericardial diseases, atrial fibrillation, myocarditis, and cardioversion. Noncardiac causes of BNP and NT-proBNP elevation include advancing age, renal failure, anemia, pulmonary diseases, sepsis, critical illness, etc [33,34]. BNP or N-terminal pro-BNP are elevated in most patients with takotsubo syndrome, and according to the International Takotsubo Registry study, BNP levels were elevated in 82.9 percent of patients with TC, with a median elevation of 6.12 times the upper limit of normal (interquartile range 2.12 to 15.70) [6, 35]. It is important to note that cardiac indices do not correlate with BNP levels, and there is a higher elevation of BNP in TC compared to ACS [36].

Compared to ACS patients, TC has a lesser degree of elevation in the markers of myonecrosis such as myoglobin, creatine kinase and troponin I and T [20]. Certain studies have suggested threshold values for troponin to rule out TC while other studies have negated it [12, 37]. In TC, the level of creatine kinase elevation is generally mild to none, Gianni et al. found the median creatine kinase to be 0.85 times the upper limit of normal with an interquartile range of 0.52 to 1.48 [38].

The InterTAK Registry for takotsubo syndrome compared matched cohorts of 455 TC and 455 ACS patients [39]. The Registry was designed to collect baseline and follow-up data on patients diagnosed with TC. According to the study, there was no significant difference in the median troponin levels in TC and ACS. However, the difference in the levels of CK and BNP was noteworthy.

InterTAK diagnostic score was developed using a derivation cohort of TC patients recruited from the InterTAK registry and patients of ACS from a Zurich hospital (TC, n = 218; ACS, n = 436).

It is helpful in predicting the probability of a diagnosis of TC and differentiating it from its major differential diagnosis i.e. ACS. The score has seven clinical variables: female sex, emotional trigger, physical trigger, the absence of ST-segment depression (except in lead aVR), psychiatric disorders, neurologic disorders, and QTc prolongation. There is a maximum score of 100. However, a cut-off value of 40 score points yields a sensitivity of 89% and specificity 91%.

The role for catecholamines in TC has been hypothesized in light of studies in which plasma catecholamines were measured at presentation [38, 40]. Two possible explanations have been proposed for the role of catecholamines in TC: 1) Myocardial stunning due to diffuse catecholamine-induced microvascular spasm [38]; 2) Myocardial toxicity due to the direct effect of catecholamines [41]. The correlation of NT-proBNP/BNP levels with both the extent of plasma normetanephrine increase and decrease of LV ejection fraction has been reported by Nguyen et al [42].

LV dysfunction in TC could be identified by echocardiography or left ventriculography. Other echocardiographic findings include basal hyperkinesis, reversible wall motion abnormalities extending beyond the distribution of an epicardial coronary artery, LV outflow tract obstruction [6, 19, 43]. Right Ventricle (RV) basal hyperkinesis and hypokinesis of RV apex with reverse Mcconnell's sign have been described in TC as well [44]. Coronary angiogram findings in TC include normal vessels or mild to moderate coronary atherosclerosis, without the presence of a ruptured plaque [18, 45, 46].

MRI imaging may be helpful in the diagnosis of TC if echocardiogram is technically suboptimal or if there is coexistent coronary artery disease. In comparison to ACS, Late Gadolinium Enhancement (LGE) is generally absent on CMR in stress Cardiomyopathy [47]. However, if CMR is performed in the acute phase (< 72 h), LGE is occasionally detected [11]. Studies of TC cases undergoing myocardial PET have identified a reverse perfusion-metabolism mismatch with normal perfusion, and reduced 18F-fluorodeoxyglucose (FDG) uptake [48].

Several ECG abnormalities can potentially help differentiate TC from ACS. According to the International Takotsubo Registry study, 43.7% of patients have ST-segment elevation. ST-segment elevation occurs most commonly in the anterior precordial leads. ST depression is a less common finding among patients with TC [6]. Other ECG findings in TC include widespread T wave inversions, low QRS voltage on presentation, attenuation of QRS voltage in serial ECGs, QTc prolongation [49, 50].

CONCLUSION

The initial diagnosis of TC remains a challenge due to the symptomatic overlap with ACS. Differentiating factors include relatively higher NP levels in TC compared to higher levels of troponin in ACS. LV dysfunction in TC can be identified by echocardiography or left ventriculography. However, the precise pathophysiological mechanism behind the symptoms of TC remains unknown and additional testing is suggested just when the diagnosis is uncertain.

REFERENCES

1. Sato H, Tateishi H, Uchida T. Takotsubo-type cardiomyopathy due to multivessel spasm. In: Kodama K, Haze K, Hon M, editors. Clinical Aspect of Myocardial Injury: From Ischemia to Heart Failure. Tokyo, Japan: Kagakuhyouronsha.1990: 56-64.

2. Sharkey SW, Windenburg DC, Lesser JR, Maron MS, Hauser RG, Lesser JN, Haas TS, Hodges JS, Maron BJ. Natural history and expansive clinical profile of stress (tako-tsubo) cardiomyopathy. J Am Coll Cardiol. 2010; 55: 333–341.

3. 3.Deshmukh A, Kumar G, Pant S, Rihal C, Murugiah K, Mehta JL. Prevalence of Takotsubo cardiomyopathy in the United States. Am Heart J. 2012; 164: 66-71.

4. Donohue D, Movahed MR. Clinical characteristics, demographics and prognosis of transient left ventricular apical ballooning syndrome. Heart Fail Rev. 2005; 10: 311-316.

5. Khera R, Light-McGroary K, Zahr F, Horwitz PA, Girotra S. Trends in hospitalization for takotsubo cardiomyopathy in the United States. Am Heart J. 2016; 172: 53-63.

6. Templin C, Ghadri JR, Diekmann J, et al. Clinical Features and Outcomes of Takotsubo (Stress) Cardiomyopathy. N Engl J Med. 2015; 373: 929-38.

7. Aizawa K, Suzuki T. Takotsubo cardiomyopathy: Japanese perspective. Heart Fail Clin. 2013; 9: 243-247.

8. Nascimento FO, Larrauri-Reyes MC, Santana O, Perez-Caminero M, Lamas GA. Comparison of stress cardiomyopathy in Hispanic and non-Hispanic patients. Rev Esp Cardiol (Engl Edn). 2013; 66: 67–68.

9. Y-Hassan S, Tornvall P. Epidemiology, pathogenesis, and management of takotsubo syndrome. Clin Auton Res. 2018; 28: 53-65.

10. Redfors B, Vedad R, Angerås O, et al.Mortality in takotsubo syndrome is similar to mortality in myocardial infarction - A report from the SWEDEHEART registry. Int J Cardiol. 2015; 185: 282-289.

11. Eitel I, von Knobelsdorff-Brenkenhoff F, Bernhardt P, et al. Clinical characteristics and cardiovascular magnetic resonance findings in stress (takotsubo) cardiomyopathy. JAMA. 2011; 306: 277-286.

12. BG Song, Chun WJ, Park YH, et al.The clinical characteristics, laboratory parameters, electrocardiographic, and echocardiographic findings of reverse or inverted takotsubo cardiomyopathy: comparison with mid or apical variant. Clin Cardiol. 2011; 34: 693-699.

13. Lyon AR, Rees PS, 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: 22-29.

14. YH S, De Palma R. Contemporary review on the pathogenesis of takotsubo syndrome: the heart shedding tears: norepinephrine churn and foam at the cardiac sympathetic nerve terminals. Int J Cardiol. 2016; 228: 528–536.

15. Obunai K, Misra D, Van Tosh A, Bergmann SR. Metabolic evidence of myocardial stunning in takotsubo cardiomyopathy: a positron emission tomography study. J Nucl Cardiol. 2005; 12: 742-744.

16. Hussain MA, Cox AT, Bastiaenen R, Prasad A. Apical ballooning (takotsubo) syndrome with concurrent ST-segment elevation myocardial infarction. BMJ Case Rep. 2017; 2017.

17. Hurtado Rendón IS, Alcivar D, Rodriguez-Escudero JP, Silver K. Acute Myocardial Infarction and Stress Cardiomyopathy Are Not Mutually Exclusive. Am J Med. 2018; 131: 202-205.

18. 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: 408-417.

19. Bybee KA, Kara T, Prasad A, Lerman A, Barsness GW, Wright RS, Rihal

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CS. Systematic review: transient left ventricular apical ballooning: a syndrome that mimics ST-segment elevation myocardial infarction. Ann Intern Med. 2004; 141: 858-865.

20. Gopalakrishnan P, Zaidi R, Sardar MR. Takotsubo cardiomyopathy: Pathophysiology and role of cardiac biomarkers in differential diagnosis. World J Cardiol. 2017; 9: 723-730.

21. Yalta K. Serum copeptin/NT-proBNP ratio: a more reliable index of absolute endogenous stress and prognosis during the course of Takotsubo cardiomyopathy? Int J Cardiol. 2012; 154: 376-377.

22. Gaddam S, Nimmagadda KC, Nagrani T, et al. Serum lipoprotein levels in takotsubo cardiomyopathy vs. myocardial infarction. Int Arch Med. 2011; 4: 14.

23. Kobayashi N, Hata N, Kume N, et al. Soluble lectin-like oxidized LDL receptor-1 and high-sensitivity troponin T as diagnostic biomarkers for acute coronary syndrome. Improved values with combination usage in emergency rooms. Circ J. 2011; 75: 2862-2871.

24. Zhong Y, Wang N. Other diagnostic methods with high sensitivity can be used to differentiate Takotsubo cardiomyopathy from acute coronary syndrome. Int J Cardiol. 2016; 222: 1068.

25. Yang HS, Kim HJ, Shim HJ, Kim SJ, Hur M, Di Somma S; GREAT Network. Soluble ST2 and troponin I combination: Useful biomarker for predicting development of stress cardiomyopathy in patients admitted to the medical intensive care unit. Heart Lung. 2015; 44: 282-288.

26. Wilkins MR, Redondo J, Brown LA. The natriuretic-peptide family. Lancet. 1997; 349: 1307-1310.

27. Volpe M, Rubattu S, Burnett J Jr. Natriuretic peptides in cardiovascular diseases: current use and perspectives. Eur Heart J. 2014; 35: 419-425.

28. Pucci A, Wharton J, Arbustini E, Grasso M, Diegoli M, Needleman P, Viganò M, Moscoso G, Polak JM. Localization of brain and atrial natriuretic peptide in human and porcine heart. Int J Cardiol. 1992; 34: 237-247.

29. Calzetta L, Orlandi A, Page C, Rogliani P, Rinaldi B, Rosano G, Cazzola M, Matera MG. Brain natriuretic peptide: Much more than a biomarker. Int J Cardiol. 2016 Oct 15;221:1031-8. doi: 10.1016/j.ijcard.2016.07.109

30. Potter LR. Natriuretic peptide metabolism, clearance and degradation. FEBS J. 2011; 278: 1808-1817.

31. Schrier RW, Abraham WT. Hormones and hemodynamics in heart failure. N Engl J Med. 1999; 341: 577-585.

32. Woodard GE, Rosado JA. Recent advances in natriuretic peptide research. J Cell Mol Med. 2007; 11: 1263-1271.

33. Tsai S-H, Lin Y-Y, Chu S-J, Hsu C-W, Cheng S-M. Interpretation and Use of Natriuretic Peptides in Non-Congestive Heart Failure Settings. Yonsei Medical Journal. 2010; 51: 151-163.

34. Zakynthinos E, Kiropoulos T, Gourgoulianis K, Filippatos G. Diagnostic and prognostic impact of brain natriuretic peptide in cardiac and noncardiac diseases. Heart Lung. 2008; 37: 275-285.

35. Madhavan M, Borlaug BA, Lerman A, Rihal CS, Prasad A. Stress hormone and circulating biomarker profile of apical ballooning syndrome (Takotsubo cardiomyopathy): insights into the clinical significance of B-type natriuretic peptide and troponin levels. Heart. 2009; 95: 1436-1441.

36. Ahmed KA, Madhavan M, Prasad A. Brain natriuretic peptide in apical ballooning syndrome (Takotsubo/stress cardiomyopathy): comparison with acute myocardial infarction. Coron Artery Dis. 2012; 23: 259-264.

37. Ramaraj R, Sorrell VL, Movahed MR. Levels of troponin release can aid in the early exclusion of stress-induced (takotsubo) cardiomyopathy. Exp Clin Cardiol. 2009; 14: 6-8.

38. Gianni M, Dentali F, Grandi AM, Sumner G, Hiralal R, Lonn E. Apical ballooning syndrome or takotsubo cardiomyopathy: a systematic review. Eur Heart J. 2006; 27: 1523-1529.

39. Ghadri JR, Cammann VL, Jurisic S, et al; InterTAK co-investigators. A novel clinical score (InterTAK Diagnostic Score) to differentiate takotsubo syndrome from acute coronary syndrome: results from the International Takotsubo Registry. Eur J Heart Fail. 2017; 19: 1036-1042.

40. Wittstein IS, Thiemann DR, Lima JA, Baughman KL, Schulman SP, Gerstenblith G, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. N Engl J Med. 2005; 352: 539-548.

41. Nef HM, Möllmann H, Kostin S, Troidl C, Voss S, Weber M, Dill T, et al. Tako-Tsubo cardiomyopathy: intraindividual structural analysis in the acute phase and after functional recovery. Eur Heart J. 2007; 28: 2456-2464.

42. Nguyen TH, Neil CJ, Sverdlov AL, et al. N-terminal pro-brain natriuretic protein levels in takotsubo cardiomyopathy. Am J Cardiol. 2011; 108: 1316-1321.

43. Tsuchihashi K, Ueshima K, Uchida T, et al; Angina Pectoris-Myocardial Infarction Investigations in Japan. 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: 11-18.

44. Liu K, Carhart R. "Reverse McConnell's sign?": a unique right ventricular feature of Takotsubo cardiomyopathy. Am J Cardiol. 2013; 111: 1232-1235.

45. Hoyt J, Lerman A, Lennon RJ, Rihal CS, Prasad A. Left anterior descending artery length and coronary atherosclerosis in apical ballooning syndrome (Takotsubo/stress induced cardiomyopathy). Int J Cardiol. 2010; 145: 112-115.

46. Prasad A, Dangas G, Srinivasan M, Yu J, Gersh BJ, Mehran R, Stone GW. Incidence and angiographic characteristics of patients with apical ballooning syndrome (takotsubo/stress cardiomyopathy) in the HORIZONS-AMI trial: an analysis from a multicenter, international study of ST-elevation myocardial infarction. Catheter Cardiovasc Interv. 2014; 83: 343-348.

47. Avegliano G1, Huguet M, Costabel JP, Ronderos R, Bijnens B, Kuschnir P, et al. Morphologic pattern of late gadoliniumenhancement in Takotsubo cardiomyopathy detected by early cardiovascular magnetic resonance. Clin Cardiol. 2011; 34: 178-182.

48. Testa M, Feola M. Usefulness of myocardial positron emission tomography/nuclear imaging in Takotsubo cardiomyopathy. World J Radiol. 2014; 6: 502-506.

49. Looi JL, Wong CW, Lee M, Khan A, Webster M, Kerr AJ. Usefulness of ECG to differentiate Takotsubo cardiomyopathy from acute coronary syndrome. Int J Cardiol. 2015; 199: 132-140.

50. Madias JE. Transient attenuation of the amplitude of the QRS complexes in the diagnosis of Takotsubo syndrome. Eur Heart J Acute Cardiovasc Care. 2014; 3: 28-36.

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