Review Article

Perioperative Takotsubo Cardiomyopathy: Implications for Anesthesiologist

Abstract

Takotsubo cardiomyopathy (TCM) is characterized by transient ventricular dysfunction in the absence of obstructive coronary artery disease that may be triggered by an acute medical illness or intense physical or emotional stress. TCM is often confused with acute myocardial infarction given the similar electrocardiographic changes, cardiac enzymes, hemodynamic perturbations, and myocardial wall motion abnormalities. In the perioperative setting, the clinical picture may be more confusing because of the effect of anesthesia as well as hemodynamic changes related to the surgery itself. However, awareness of various other diagnostic modalities may enable clinicians to distinguish between the two, more systematically and with greater certainty. Despite the large body of literature, there still seems to be an overall paucity in our understanding of the etiopathogenesis, clinical characteristics, natural history, and management of this syndrome, especially in the perioperative setting. This narrative review seeks to present and synthesize the most recent literature on TCM and to identify gaps in current knowledge which can become the basis for future research.

Keywords: *Perioperative, stress, surgery, takotsubo cardiomyopathy*

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Introduction

Takotsubo cardiomyopathy (TCM) refers to a syndrome characterized by transient left ventricular (LV) dysfunction but without evidence of obstructive coronary artery disease (CAD).[1] First described in the 1990s in Japan delineating a stunned myocardium in the setting of multivessel coronary artery spasm,[2] "takotsubo" refers to Japanese ceramic pot used to trap octopuses, which resembles the most common LV conformation associated with this disorder, with apical akinesis and basal hyperkinesis.[3] As the reported incidence of this cardiomyopathy has since risen worldwide, it has taken on multiple names such as apical ballooning syndrome, broken heart syndrome, and stress-induced cardiomyopathy. Stressors that can trigger this cardiomyopathy may be emotional or physical.[4] It has been noted in outpatient and inpatient scenarios, critical care units, and the perioperative environment.[5] This narrative review is an attempt to synthesize the literature and identify gaps in our current understanding of the pathophysiology, clinical characteristics, natural history, and management of this syndrome, especially in the perioperative setting.

For this review, a MEDLINE database search was performed using the following Medical Subject Headings terms: takotsubo cardiomyopathy, ampulla cardiomyopathy, anesthesia cardiomyopathy, broken heart syndrome, stress-induced cardiomyopathy, transient left ventricular apical ballooning syndrome, and transient midventricular ballooning. These were combined with the following: anaesthesia, anesthesia, intraoperative, perioperative, postoperative, after surgery, and during surgery. A Web of Science search was then performed using similar terms. Additional references were then identified by manual search of the articles obtained from MEDLINE and Web of Science. With the exception of a 1991 publication, the searches covered the period from January 2000 to February 2018.

Diagnosis

Numerous diagnostic criteria have been proposed for TCM[4,6-12] [Table 1]; however, the revised Mayo Clinic criteria published in 2008[7] is still the most widely cited and probably the criteria against which most scientific work has been compared. While the recent European Society of

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Table 1: Perioperative triggers of takotsubo cardiomyopathy

Year	Diagnostic criteria
2004	Mayo clinic criteria[4]
	All four of the following criteria
	1. Transient LV apical and midventricular segmental akinesis or dyskinesis with RWMAs extending beyond a single epicardial vascular distribution
	2. Absence of obstructive CAD or angiographic evidence of acute plaque rupture
	3. New EKG abnormalities (either ST-segment elevation or T-wave inversion)
	4. Absence of recent significant head trauma, intracranial bleeding, pheochromocytoma, obstructive CAD, myocarditis, and hypertrophic cardiomyopathy
2007	Japanese criteria[6]
	1. LV takes on classic takotsubo shape
	2. Dynamic obstruction of the LV outflow track
	3. Recovery of the LV apical akinesis within 1 month
	4. Absence of significant obstructive CAD, cerebrovascular disease, myocarditis, and pheochromocytoma
2008	Revised Mayo clinic criteria[7]
	1. Transient LV midsegments hypokinesis, akinesis, or dyskinesis that extends beyond a single epicardial vascular distribution. A stressful trigger and apical involvement may or may not be present
	2. Absence of obstructive CAD or angiographic evidence of acute plaque rupture
	3. New electrocardiographic changes, that is, ST-segment elevation and/or T-wave inversion or elevated troponin level
	4. Exclusion of pheochromocytoma and/or myocarditis
2011	Gothenburg criteria[8]
	1. Transient LV hypokinesis, akinesis, or dyskinesis and frequently, but not always, a stressful trigger (psychological or physical)
	2. Absence of other pathological conditions (e.g., ischemia, myocarditis, toxic damage, and tachycardia) to explain the regional dysfunction
	3. No elevation or modest elevation in cardiac troponin (i.e., disparity between the troponin level and the amount of dysfunctional myocardium
2012	Johns Hopkins criteria[9]
	Helpful, but not mandatory, criteria
	1. An acute identifiable trigger (either emotional or physical)
	2. Characteristic ECG changes that may include some or all of the following: ST-segment elevation and/or T-wave inversion and/or QT-interval prolongation
	3. Mildly elevated cardiac troponin (often appears disproportionately low given the degree of wall motion abnormality)
	Mandatory criteria (all three criteria must be met)
	1. Absence of obstructive CAD or angiographic evidence of acute plaque rupture
	2. Regional ventricular wall motion abnormalities that extend beyond a single epicardial vascular distribution
	3. Complete recovery of RWMAs (recovery is usually within days to weeks)
2013	Revised Gothenburg criteria[10]
	1. Transient LV hypokinesis, akinesis, or dyskinesis and frequently, but not always, a stressful trigger (psychological or physical)
	2. Absence of other pathological conditions (e.g., ischemia, myocarditis, toxic damage, and tachycardia) to explain the regional dysfunction
	3. No elevation or modest elevation in cardiac troponin (i.e., disparity between the troponin level and the amount of dysfunctional myocardium)
	4. Normal or near-normal LV filling pressures
2014	Italian network criteria[11]
	Mandatory criteria
	1. Transient LV wall motion abnormalities extending beyond a single epicardial vascular distribution with complete functional normalization within 6 weeks
	2. Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture dissection, thrombosis, or spasm
	3. New ECG abnormalities (either ST-segment elevation or T-wave inversion or left bundle-branch block)
	4. Mild increase in myocardial injury markers (creatine kinase [MB fraction] <50 U/L)
	5. Exclusion of myocarditis
	Optional criteria
	1. Postmenopausal woman
	2. Presence of a stressful trigger

Contd...

Table 1: Contd...

Year	Diagnostic criteria
2016	Heart Failure Association of the European Society of Cardiology criteria[12] 1. Transient LV or RV RWMAs which are frequently, but not always, preceded by a stressful trigger (emotional or physical). 2. RWMAs usually[a] extend beyond a single epicardial vascular distribution and often result in circumferential dysfunction of the ventricular segments involved. 3. Absence of culprit atherosclerotic CAD including acute plaque rupture, thrombus formation, and coronary dissection or other pathological conditions to explain the pattern of temporary LV dysfunction observed (e.g., hypertrophic cardiomyopathy and viral myocarditis). 4. New and reversible EKG abnormalities (ST-segment elevation, ST depression, LBBB[b], T-wave inversion, and/or QTc prolongation) during the acute phase (3 months) 5. Significantly elevated serum natriuretic peptide (BNP or NT-proBNP) during the acute phase 6. Positive but relatively small elevation in cardiac troponin measured with a conventional assay (i.e., disparity between the troponin level and the amount of dysfunctional myocardium present)[c] 7. Recovery of ventricular systolic function on cardiac imaging at follow-up (3-6 months)[d]

[a]Acute, reversible dysfunction of a single coronary territory has been reported, [b]LBBB may be permanent after Takotsubo syndrome but should also alert clinicians to exclude other cardiomyopathies. T-wave changes and QTc prolongation may take many weeks to months to normalize after recovery of LV function, [c]Troponin-negative cases have been reported but are atypical, [d]Small apical infarcts have been reported. Bystander subendocardial infarcts have been reported, involving a small proportion of the acutely dysfunctional myocardium. These infarcts are insufficient to explain the acute RWMA observed. LV: Left ventricular, RWMAs: Regional wall motion abnormalities, CAD: Coronary artery disease, RV: Right ventricular, LBBB: Left bundle branch block, BNP: B-type natriuretic peptide, NT-proBNP: N-terminal proBNP

Cardiology Criteria[12] has more comprehensive and extensive factors, it has yet to achieve widespread acceptance. Furthermore, there is often confusion between acute myocardial infarction (AMI) and TCM given the similarities in electrocardiographic (EKG) changes, cardiac enzymes, hemodynamic perturbations, and myocardial wall motional abnormalities. However, a deeper insight into the differences noted on various diagnostic modalities can help distinguish TCM from AMI.

Electrocardiographic changes

A combination of ST-segment depression >0.5 mm in lead aVR and ST-segment elevation ≤1 mm in lead V_1 has shown very high sensitivity (91%), specificity (96%), and positive predictive accuracy (95%) in identifying TCM.[13] However, these findings could not be reaffirmed in subsequent studies by Johnson *et al*.[14] (0%, 99%, and 88%) and Vervaat *et al*.[15] (26%, 96%, and 76%), who found high specificity but extremely low sensitivity and slightly lower positive predictive values. Some investigators found a lower maximal ST elevation (2 mm vs. 3 mm) in a greater number of leads with ST elevation in TCM patients compared with those with AMI.[13,16]

A recent study by Namgung found two different EKG patterns representative of TCM: ST elevation followed by T-wave inversions after ST elevations have subsided and more commonly T-wave inversions alone without associated ST elevations but associated with QTc prolongations.[17] This suggests that reviewing the timeline of EKG changes may be more valuable than a single snapshot (i.e., EKG at initial presentation).

In the perioperative period, electrolyte abnormalities can occur, which may influence and/or mask EKG findings. Along with that, for a true intraoperative event, obtaining a 12-lead EKG may not be immediately feasible, and since the consequences of a missed diagnosis of AMI can be omnious, it may be necessary to include other parameters to guide the diagnosis of TCM.

Cardiac enzymes

In most cases of TCM, cardiac biomarkers are elevated. In the large International Takotsubo Registry, a consortium of 26 centers in Europe and the United States, median troponin levels on admission were 7.7 times the normal range and creatinine kinase levels were normal or slightly elevated at 0.85 times the normal range. It is important, however, to note that the troponin elevation was much lower in TCM as compared to AMI.[18,19]

Recently, a new noninvasive tool called the troponin-ejection fraction product derived from the peak troponin I level and the echocardiographically derived LV ejection fraction has been developed and tested for patients who for whatever reason do not undergo emergent angiography.[20] A value ≥250 had a high overall accuracy of 91% to differentiate an AMI from a TCM.[20] Several other biomarkers in the combination including the ratio of the N-terminal prohormone of brain natriuretic peptide over myoglobin or troponin T may also aid in this differentiation.[21]

Echocardiographic findings

Transthoracic echocardiography, or in the perioperative setting, transesophageal echocardiography, is usually the first noninvasive imaging technique used to diagnose TCM. This is done to assess LV function and the pattern of regional wall motion abnormalities (RWMAs) to help identify TCM variants. It also aids in early recognition of any LV outflow tract obstruction and/or mitral regurgitation, which may influence management and outcomes.[22,23]

The classic RWMAs associated with TCM include systolic mid-LV and apical hypokinesis or dyskinesis with preservation or hypercontractility of the LV basal segments. The LV dysfunction usually extends beyond a single coronary artery distribution. This produces the apical ballooning that is characteristically identified with TCM. Some variants of this presentation include midventricular, basal, focal, or global hypokinesis.[18] While most TCM cases have transient LV systolic dysfunction, however, right ventricular involvement has been noted in 25%–42% of the TCM population.[24,25]

Coronary angiography and other imaging modalities

Given the similarity in presentations between AMI and TCM, it is important to obtain appropriate imaging that will assist in ruling out obstructive CAD to guide the necessary intervention. Cardiac catheterization has been utilized as a confirmatory test for the diagnosis of TCM. In patients with TCM, coronary angiography will most likely reveal normal coronary arteries. It is important to note that 10% of TCM cases may also have coexisting obstructive CAD.[26] Therefore, delineating whether the obstructive lesion is the cause of the RWMA becomes vital to determine which management strategy needs to be employed.[23]

In cases with coexistent CAD or an echocardiogram with poor visualization, cardiovascular magnetic resonance (CMR) imaging can be utilized.[27] The absence of late gadolinium enhancement on CMR provides evidence against AMI and myocarditis.[28] CMR can help identify a ventricular thrombus or involvement of the right ventricle that may not be easily visualized on echocardiogram.[24,29] An imaging technique, but one that is not as widely used for the diagnosis of TCM, is positron-emission tomography. A phenomenon known as "inverse flow-metabolism mismatch" due to a discrepancy between normal perfusion and limited glucose metabolism in dysfunctional areas is seen in myocardial positron-emission tomographic scans of TCM patients.[30]

Demographics

As per a registry of 3265 patients, approximately 1% of patients presenting with acute coronary syndrome were found to have TCM.[31] Based on the estimated US census in 2008 and Nationwide Inpatient Sample database, there is a stronger overall female predominance for TCM (5.2 per for every 100,000 females versus 0.6 for every 100,000 males).[32] This was further corroborated by the 84.3% incidence in females of perioperative TCM as reported by Agarwal *et al*., with a similar higher proportion in the elderly age bracket.[33] Furthermore, similar to nonperioperative TCM, a stronger Caucasian predilection was observed in those presenting in the perioperative period.[33]

Etiopathogenesis

Defining the specific pathogenesis for TCM has been an elusive task. Multiple theories have been proposed including coronary artery vasospasm, microvascular dysfunction, and postacute coronary syndrome reperfusion injury.[34-36] One of the most prominent theories focuses on excess catecholamine surge during emotional or physical stress activating beta- and alpha-adrenergic receptors and causing microvascular spasm that eventually precipitates myocyte injury.[37,38] This is supported by myocardial biopsies showing contraction band necrosis, inflammatory cell infiltration, and interstitial fibrosis; these histological findings are associated with catecholamine-induced injury.[39]

Furthermore, given the predilection of TCM among postmenopausal women, a lack of estrogen has been considered a significant risk factor. Estrogen induces production of heat shock protein and atrial natriuretic peptide, both of which are thought to be cardioprotective against the adverse effects of catecholamine surge and oxidative stress.[40] A systematic literature review found that none of the cases of TCM was being treated with estrogen replacement therapy.[41]

Myocardial oxidative stress may be another contributory factor for the transient LV dysfunction noted in TCM. Nanno *et al*. noted elevated levels of 8-hydroxy-2′-deoxyguanosine (used as a marker of oxidative stress) associated with increased levels of norepinephrine in TCM patients.[42] Furthermore, oxidative stress causes upregulation of heme oxygenase-1 in cardiac and aortic macrophages secondary to catecholamine crisis in animal models of TCM.[43] Myocardial injury could be purported due to free radical regeneration, calcium overload, and calcium retention in the sarcoplasmic reticulum causing excitation–contraction uncoupling.[29]

A recently published systematic review of TCM cases reported that surgery can be psychologically and emotionally taxing[33] and that numerous nonpsychological factors in the perioperative period may contribute to the development of this condition [Table 2].[44-53] However, given the intense stress experienced by most patients undergoing surgery, and the large number of surgeries being performed across the world, cardioprotective effects of volatile agents may have a bearing on the relatively low incidence of perioperative TCM. While there is now a body of evidence from animal and *in vitro* studies of human myocardial tissue suggestive of ischemic preconditioning properties of volatile anesthetics,[54] its actual role in the pathogenesis and prevention of perioperative TCM needs further exploration.

Furthermore, given that only a miniscule proportion of all the perimenopausal women undergoing surgery develop TCM, there has been some recent interest toward delineating the role of genetics in this condition. This

Table 2: Comprehensive timeline of diagnostic criteria for takotsubo cardiomyopathy

Perioperative triggers[44-53]
1. Inadequate depth of anesthesia (local or general)
2. Tracheal manipulation during intubation and extubation
3. Parasympathetic denervation in the area of the pulmonary veins post radiofrequency ablation for atrial fibrillation
4. An exaggerated response to catecholamines due to selective sympathetic reinnervation in a transplanted heart
5. Exogenous administration of epinephrine or other catecholamines
6. Release of inflammatory mediators due to anaphylaxis (Kounis syndrome)
7. Abnormal myocardial functional architecture that predisposes patients to LV outflow obstruction in the presence of hypovolemia and/or high intrinsic or extrinsic catecholamine load
8. Extreme hemodynamic and pulmonary compromise in the perioperative period
9. Excessive CO_2 absorption during laparoscopic surgery
10. Use of ergometrine after cesarean sections
11. Cardiac arrest due to other causes
12. Direct spinal cord stimulation during placement/removal of spinal cord stimulators
13. Autonomic dysregulation during and/or after electroconvulsive therapy

LV: Left ventricular

interest has stemmed largely from reports of familial cases of TCM, nonstress triggered TCM (especially in premenopausal females), and recurring TCM episodes.[55-58] Polymorphisms in genes for the alpha 1-, beta 1-, and beta 2-adrenergic receptors as well as the G protein-coupled receptor kinase 5 are being investigated for a link to TCM; however, no conclusive evidence has been found.[58-60] Eitel *et al*. recently conducted the first genome-wide association study for TCM locating 68 candidate loci,[61] and some preliminary studies have also reported an association with estrogen receptor polymorphisms in both the ESR1 and ESR2 genes.[62] However, it is important to note that larger population studies are necessary to provide statistically significant genetic links for TCM.

Management and Prognosis

Randomized controlled trials of specific therapeutic strategies are lacking, and thus, TCM management is driven by the understanding of the pathophysiology.[7,63] Given the reversible effects of cardiac injury, the interim management focuses on supportive care and prevention of severe complications.[64] Initial management of acute-phase TCM is similar to AMI given the similarity in presentation with aspirin, heparin, and antiplatelet therapy. Hemodynamically stable patients are managed with beta-blockers, angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin-receptor blockers (ARBs), and diuretics. For patients with severe LV outflow obstruction, treatment involves beta-blockers, α-agonists, and/or calcium channel blockers along with volume expansion; nitrites and inotropic agents are avoided in this scenario. Furthermore, anticoagulation may be initiated for patients with apical dysfunction for the prevention of thrombus formation.[36] For severely unstable patients, intra-aortic balloon pump along with extracorporeal membrane oxygenation or temporary ventricular-assisted devices may be necessary.[65]

Perioperative management of TCM involves an intricate interplay of several key factors. Elective procedures in patients with known TCM are often delayed until resolution of the cardiomyopathy. If psychological risk factors, e.g., death in the family or divorce, have been identified during the preoperative assessment, then delaying an elective surgery may be prudent. For nonelective cases, extra focus on allaying anxiety and stress may help in preventing a TCM episode. If feasible, regional anesthesia with appropriate sedation should be employed since it affords the ability to avoid general anesthesia-associated stress (with intubation and extubation) and provides postoperative pain control.[66] Irrespective of the anesthetic management employed, avoidance of stressors that could trigger a catecholamine surge is vital through appropriate pain management and preoperative anxiolysis as well as smooth induction and emergence. Prophylactic beta-blocker therapy should be given. Furthermore, invasive monitoring may be required including arterial line and transthoracic or transesophageal echocardiography. Many of these patients may require observation overnight in an intensive care unit given the potential for a TCM episode in the immediate postoperative period.[23,67]

Although a favorable prognosis and fast recovery are observed for most patients with TCM that survive the acute episode, it is important to note that mortality risk in TCM is similar to patients with AMI. Templin *et al*. reported a 30-day risk of major adverse cardiac and cerebrovascular events of 5.9%. Furthermore, the mortality rate per year was 5.6%, and the rate of stroke or transient ischemic attack was 1.7%.[18] Studies indicate that the annual recurrence rate of TCM is about 1-2%, with ACEi/ARBs having a stronger impact in reduction of recurrence when compared to beta-blockers.[68]

Conclusions and Future Directions

As the body of knowledge has expanded, we have become more proficient at the diagnosis and treatment of TCM, in general, and perioperative TCM, in particular. However, well-planned controlled clinical trials are needed to test various diagnostic and treatment regimens. Clinical trials are also needed to provide sufficient evidence to enable agreement on a single set of criteria with which to define TCM along with dedicated criteria for the perioperative setting. Such rigorous testing will enable the development of guidelines to suggest treatments specific to the degree of hemodynamic stability of each individual patient. If such guidelines are followed by practitioners on a wide scale,

then not only will more patients be treated expeditiously and appropriately, but the likelihood of life-threatening cardiac and cerebrovascular events that could occur after a TCM would also be reduced. Simultaneous research to better understand the cardioprotective effects of volatile agents as well as the genetic links if any may help not only to prevent TCM perioperatively by tailoring the anesthetic management but also to aid in the identification of those susceptible to this syndrome in the future.

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Conflicts of interest

There are no conflicts of interest.

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