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MINIREVIEWS

Takotsubo cardiomyopathy: A comprehensive review

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Abstract

Takotsubo cardiomyopathy (TCM), also known as stress cardiomyopathy, occurs in the setting of catecholamine surge from an acute stressor. This cardiomyopathy mimics acute myocardial infarction in the absence of coronary disease. The classic feature of TCM is regional wall motion abnormalities with characteristic ballooning of the left ventricle. The etiology of the stressor is often physical or emotional stress, however iatrogenic causes of TCM have been reported in the literature. In our review, we discuss medications, primarily the exogenous administration of catecholamines, and a wide array of procedures with subsequent development of iatrogenic cardiomyopathy. TCM is unique in that it is transient and has favorable outcomes in most individuals. Classically, beta-blockers and ACE-inhibitors have been prescribed in individuals with cardiomyopathy; however, unique to TCM, no specific treatment is required other than temporary supportive measures as this process is transient. Additionally, no improvement in mortality or recurrence have been reported in patients on these drugs. The aim of this review is to elucidate on the iatrogenic causes of TCM, allowing for prompt recognition and management by clinicians.

Key Words: Takotsubo; Cardiomyopathy; Iatrogenic; Heart Failure; Myocardial Infarction

Core Tip: The aim of this review is to elucidate on the iatrogenic causes of Takotsubo cardiomyopathy (TCM). To date, there are individual case reports of iatrogenic TCM but there is not a comprehensive review article. In this review article, we discuss medication and procedure-induced TCM as well as an in-depth review of the current pathophysiology behind TCM.

INTRODUCTION

Takotsubo cardiomyopathy (TCM) was first identified in Japan in 1991. The term "Takotsubo" originates from the Japanese word for octopus trap as cardiac morphology in this disease process often resembles the shape of these traps. Since its identification, TCM has also been referred to as stress cardiomyopathy, apical ballooning syndrome, or broken heart syndrome. This complex disease mimics acute myocardial infarction in the absence of obstructive coronary disease and is characterized by transient left ventricular dysfunction. The main feature of TCM is regional wall motion abnormalities with a characteristic ballooning of the left ventricle during systole. The wall motion abnormalities are unique as they extend beyond a single vascular territory and are usually localized to the apex of the left ventricle; however, non-apical variants exist[1]. Although TCM itself is often underdiagnosed, its clinical relevance, recognition, and understanding have progressively accelerated in the recent years. The cardiomyopathy occurs in the setting of a catecholamine surge from an acute stress leading to cardiac dysfunction. The etiology of the stressor is often physical or emotional stress; however, less commonly iatrogenic causes of TCM have been reported as well. Iatrogenic TCM can classified as either medication or procedure related. The aim of this review article is to focus on the reported iatrogenic causes of TCM and to make clinicians aware of this disease process and its complications, allowing for prompt recognition and possibly reducing morbidity and mortality from this rare process.

CLINICAL PRESENTATION

Before discussing iatrogenic causes of TCM, it is important to review the clinical presentation of TCM. Patients frequently present with chest pain, dyspnea, and syncope, and less commonly with arrhythmias, cardiogenic shock, and cardiac arrest. These symptoms are triggered most often by acute physical or emotional stress and infrequently by medical procedures and medication administration. Patients may have elevated cardiac biomarkers (NT-proBNP, troponin T), which complicates differentiating TCM from acute myocardial infarction. High NT-proBNP/troponin T ratio has a sensitivity of 91% and specificity of 95%, is suggestive of TCM, and is helpful in differentiating TCM from ST-elevation myocardial infarction[2]. Typical electrocardiographic findings in TCM include ST-elevation, ST depression, QTc prolongation, and T-wave inversions[3]. On the echocardiogram, left ventricular dysfunction (hypokinesia, akinesia, or dyskinesia) can be observed as apical ballooning or midventricular, basal, or focal wall motion abnormalities[4]. TCM predominantly affects the apex; however, non-apical variants may occur. The incidence of such non-apical variants ranges from 8%-40%, with the mid-ventricular variant accounting for approximately 20%, and the basal form for approximately 3%[1]. This cardiomyopathy is unique because it is associated with a nonischemic etiology of acute, but transiently decreased, systolic function with wall motion abnormalities extending beyond a single vascular territory. Angiography often reveals the absence of coronary atherosclerotic disease without dissection, plaque rupture or thrombus formulation. If ventriculography is performed, an apical nipple sign (Figure 1) may be visualized with regional wall motion abnormalities. Lastly, on cardiac magnetic resonance imaging these patients often have reveal wall motion abnormalities, apical ballooning (Figure 2A), late gadolinium enhancement and edema (Figure 2B) on T2 weighted imaging in the dysfunctional left ventricle (LV) regions[1]. Therefore, given that its presentation can mimic that of an acute myocardial infarction, it is critical to diagnose and treat this disease appropriately to allow for rapid recovery and improve long term outcomes in patients.

PATHOPHYSIOLOGY

The pathophysiology of TCM is not completely understood. One of the most well-known and accepted hypotheses concerning the etiology of ventricular dysfunction in this condition is the catecholamine theory[5]. Amariles and Cifuentes suggested that acute stressors lead to an increase in the concentration of neuropeptides and catecholamines (dopamine, epinephrine, norepinephrine) during the acute phase of TCM, contributing to LV dysfunction[6]. These elevated levels of catecholamines contribute not only to myocardial dysfunction, but also cause coronary microvascular vasospasm, increasing cardiac workload and leading to a supply-demand mismatch. This acute mismatch is followed by post-ischemic stunning of the myocardium, resulting in the typical apical ballooning the left ventricle. However, the
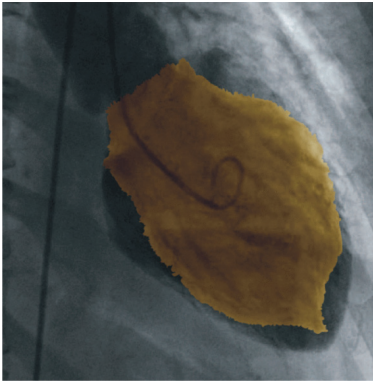
Figure 1 Ventriculogram with apical ballooning with presence of apical nipple sign[31]. Citation: Walter Desmet, Johan Bennett, Bert Ferdinande, Dries De Cock, Tom Adriaenssens, Mark Coosemans, Peter Sinnaeve, Peter Kayaert, Christophe Dubois. The apical nipple sign: a useful tool for discriminating between anterior infarction and transient left ventricular ballooning syndrome. *Eur Heart J Acute Cardiovasc Care* 2013; 3: 264-267. Copyright The European Society of Cardiology 2013. Published by Oxford University Press.
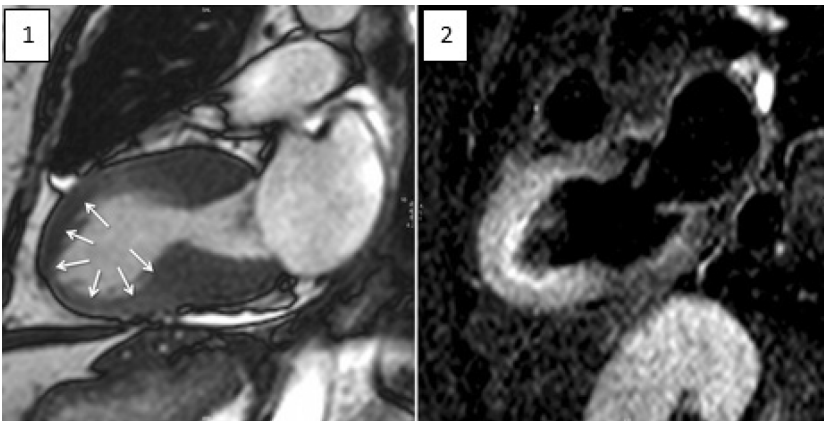

Figure 2 Cardiac magnetic imaging noting (1) apical ballooning (2) myocardial edema in the mid-apical region of the left ventricle[36]. Citation: Plácido R, Cunha Lopes B, Almeida AG. The role of cardiovascular magnetic resonance in takotsubo syndrome. *J Cardiovasc Magn Reson* 2017; 18: 68. Copyright The Authors 2017. Published by Springer Nature.

stunning is temporary and the transient ballooning and is typically followed by complete recovery of the left ventricular contractility after a short period of time in most cases.

In TCM, stress leads to an acute increase in primarily two catecholamines, norepinephrine and epinephrine. Most of the norepinephrine and all of the epinephrine is released from the adrenal medulla [7]. Interestingly, only some of these secreted catecholamines are released into the circulation; most is released directly by the sympathetic nerve endings into the nerve terminals and is presented directly to the adrenoreceptors in the myocardium. This direct release of catecholamines into the myocytes leads to decreased myocardial viability through cAMP mediated calcium overload resulting in myocardial toxicity and myocardial contraction band necrosis[8]. Similar toxicity and necrosis is seen in acute neurovascular events such as subarachnoid hemorrhage as well as in patients with pheochromocytoma, and those dying from violent assaults, or drowning, thus confirming the link between acute stress and cardiac injury[8]. The pattern of contraction band necrosis is considered one of the hallmark signs of TCM[9].

A protective method that the myocardium implements against excessive catecholamines to prevent myocardial necrosis and LV dysfunction is "stimulus-trafficking". During a catecholamine surge, myocardial adrenoreceptors undergo a switch from Gs to Gi coupling leading to a negative inotropic response[10]. If not for this switch, the catecholamine surge would activate the Gs protein pathway, causing increased myocardial contractility and workload, ultimately leading to myocardial injury and toxicity as described earlier. Additionally, the characteristic apical ballooning pattern can be explained by the regional differences in the presence of adrenoreceptors in the myocardium. B2-adrenoreceptors are more densely distributed in the apical region than the basal segment of the LV, whereas B1-adrenoreceptors are expressed more at the base than the apex[11]. Therefore, with high levels of catecholamines, the classic pattern of enhanced basal contraction and reduced apical contractility is seen. This theory was confirmed in rat models in which a bolus of epinephrine to mimic a catecholamine surge resulted in reversible depression of apical contraction and basal hypercontractility[12].

In addition to activation of negative inotropic signaling, catecholamines have been shown to cause epicardial coronary vasospasm and microvascular coronary dysfunction. Decreased radioactive tracer uptake during positron emission tomography perfusion scans in the acute phase of TCM confirms the involvement of microvascular coronary dysfunction as a trigger for myocardial dysfunction[5]. Additionally, Angelini performed acetylcholine testing of the coronaries which led to transient LV dysfunction, confirming a potential role of vasospasm in TCM[13].

Lastly, estrogen deficiency has also been identified as a contributing factor to TCM. In menopause, there is an increased sympathetic drive noted from the lack of estrogen in the circulation. This increases the risk of post-menopausal females to TCM and explains the high incidence of (approximately 89.8%) of TCM in elderly women[14]. Similar to post-menopausal females, the lack of estrogen in males places them at a higher risk of developing TCM and they are noted to have worse outcomes than their female counterparts. To further support estrogen's role in TCM, animal models have demonstrated that estrogen pre-treatment prevents stress-induced LV apical ballooning[5].

CASE REPORTS: MEDICATION-INDUCED TCM

TCM has been widely reported following medication administration with a much higher incidence occurring after catecholamine administration[15-18]. Most of the case reports listed in Table 1, with the exception of Teixeria *et al*[19], discuss an acquired TCM after receiving a prolonged administration of catecholamines. Laínez *et al*[16] present the case of a 61-year-old female who was to undergo resection of a urinary neoplasm. Following anesthesia induction, she experienced fictitious hypotension that was initially believed to be anaphylactic shock. High-dose epinephrine and norepinephrine were administered, and she was found to have a new left bundle branch block on ECG. Further evaluation revealed septal, lateral, and apical dyskinesia with subsequent angiogram revealing non obstructive coronary artery disease. These findings were consistent with TCM, and she had full ventricular recovery over the following four d. As mentioned, Teixeria *et al*[19] stands alone from other case reports listed in Table 1 in that the offending agent was a beta-blocker and not a catecholamine. This case involved a 47-year-old female presenting with severe gastrointestinal symptoms who was given a beta blocker (esmolol) for sinus tachycardia and shortly thereafter developed cardiogenic shock in the setting of elevated cardiac biomarkers. Subsequent evaluation revealed nonobstructive coronaries, preserved apical contractility, and basal akinesis consistent with a non-apical TCM variant. She had full ventricular recovery over the next two d, and her clinical course is unique as it was likely the result of sympathetic stimulation from severe gastrointestinal illness and exacerbated by esmolol administration, likely mimicking the switch from Gs to Gi as seen in "stimulus-trafficking". Additional cases have been reported in the literature involving medication induced TCM following catecholamine administration and can be found in Table 1.

CASE REPORTS: PROCEDURE-INDUCED TCM

In addition to medication induced TCM, there are several cases documenting post-procedural TCM. With the exception of a patient incidentally receiving undiluted norepinephrine, Table 2 lists post-procedural development of TCM in patients who did not receive catecholamines prior to or during a procedure[20]. Table 2 highlights a wide range of procedures associated with TCM including electroconvulsive therapy, endoscopy, valve replacement and bronchoscopy. In one case report, Narayanan *et al* presented the case of a middle-aged female with refractory depression who developed TCM after receiving electroconvulsive therapy[21]. She had been receiving long term therapy with a beta-blocker (bisoprolol) and an ace-inhibitor (lisinopril), both of which were believed at that time to offer protection against the development of TCM[22]. However, Brunettii *et al*[23] subsequently reanalyzed and ultimately refuted this assertion. Most of the cases presented in Table 2 involved anesthetic induction which may have been a contributing factor in the subsequent development of TCM in these patients.

RISK FACTORS, TREATMENT AND PREVENTION

TCM is transient and has favorable outcomes in the large majority of patients. Significant adverse events such as free wall rupture, or cardiac arrest occurs infrequently. Therefore, no specific treatment is recommended. TCM has been known to have a relatively low recurrence rate, at 4% per El-battrawy *et al* [24] Beta-blockers and ACE-inhibitors (ACEi) are commonly used in patients with LV dysfunction given their cardioprotective nature; however, no consensus is available for their use in TCM. Isogai *et al*[25] established that early introduction of beta-blockers in individuals with TCM did not lower their 30-day inpatient mortality. However, lower rates of cardiac rupture were noted in patients with TCM on beta-blockers by Kumar *et al*[26].

Table 1 Medication-induced takotsubo cardiomyopathy case reports

	Sundbøll *et al* [15], 2014	Laínez *et al*[16], 2009	Azouzi *et al*[17], 2019	Ward *et al*[18], 2019	Teixeira *et al*[19], 2014
Electrocardiogram findings	STE II, III, I, aVL, V2-6	New LBBB	Anterolateral STE	TWI	QTc prolongation (479ms)
Peak troponin I (µg/L)	0.773	N/A	0.08	N/A	8.2
Echocardiogram	Apical ballooning	Septal, apical, lateral akinesia	40%; apical hypokinesis	Basal hypokinesis	Mid-to base akinesis w/severe systolic dysfunction; preserved apical contractility
Angiography	Nonobstructive	Nonobstructive	Nonobstructive	Nonobstructive	Nonobstructive
Administered medication	Mucosal E, cocaine	NE, E	E gtt(BB overdose)	NE	Esmolol
LV Recovery Time	4 d	5 d	[a]	[a]	2 d

[a]Recovered left ventricle function without documented time. N/A: Not reported; E: Epinephrine; NE: Norepinephrine; TWI: T-wave Inversion; BB: Beta-blocker; STE: ST-elevation; LV: Left ventricle.

Table 2 Iatrogenic-takotsubo cardiomyopathy after procedure case reports

	Narayanan *et al*[21], 2014	Yeow *et al* [27], 2020	Chen *et al* [20], 2011	Kim *et al* [32], 2011	Yu *et al* [33], 2016	Blázquez *et al* [4], 2010	Hui *et al*[34], 2019	Tori *et al*[35], 2008
Procedure	ECT	ECT	Percutaneous coronary intervention	Upper, lower endoscopy	Upper endoscopy	Mitral valve replacement	Bronchoscopy	cholecystectomy and choledocholithotomy
Procedure medication	Propofol, succinyl choline	N/A	Undiluted NE	Pentazocine, Midazolam	Lidocaine spray, Midazolam	N/A	N/A	N/A
Electrocardiogram findings	ST depression and TWI V5-V6	Left anterior fascicular block, TWI III	STE V2-V6	STE V2-3	normal	TWI V1-6	Anterior TWI	TWI V2-5
Peak troponin I (ng/mL)	2.847	N/A	15.11	2.0	3.79	N/A	N/A	normal
Echocardiogram	52%, mid-segment and apical hypokinesia with ballooning	Mid-ventricular and apical akinesis	20-40%, severe apical and septal hypokinesis	Hyperkinetic basal LV; rest of LV akinetic	45%, Hypokinetic mid-LV	15-20%; severe mid-ventricular dysfunction, apical akinesis, with hyperdynamic basal segments	10-15%, apical ballooning and hypokinesis	apical akinesis, basal hyperkinesis
Angiography	NOB	NOB	NOB.	NOB.	NOB.	NOB.	NOB.	N/A
LV recovery time	[a]	3 wk d	2 d	2 mo	6 d	11 d	[a]	14 d

[a]Recovered left ventricle function without documented time. N/A: Not reported; E: Epinephrine; NE: Norepinephrine; TWI: T-wave Inversion; BB: Beta-blocker; STE: ST-elevation; LV: Left ventricle; NOB: Nonobstructive.

Singh *et al*[22] performed a meta-analysis evaluating the efficacy of beta-blockers and ACEi in preventing recurrent TCM. They concluded that ACEi were superior to beta-blocker in recurrent TCM. A case report by Yeow *et al*[27] supports the use of both ACEi and beta-blockers. It involves a 61-year-old male who was admitted suicidal ideation and underwent ECT with subsequent development of TCM. This patient was started on a beta-blocker (metoprolol succinate) and ACEi (lisinopril) while hospitalized and re-evaluated in the outpatient setting three weeks later. He was found to have full ventricular recovery and underwent ECT four additional times over the following six mo without recurrence of TCM, which supports the findings of Singh *et al*[22]. However, Brunetti *et al*[23] reanalyzed the data of Singh *et al*[22] a year later, and suggested that the lower rates of TCM were noted in patients treated with ACEi than beta-blockers; however, this difference was not secondary to the drugs' cardioprotective effect, but rather due to the fact that the patients in the ACEi cohort were

prescribed the drug at a higher rate and these patients had closer follow-up than patients in the beta-blocker cohort. Lastly, a recent study by Kim *et al*[28] failed to show a survival benefit or prevent recurrence in patients with TCM treated with ACE inhibitors or beta-blockers.

A recent study by Deshmukh *et al*[29] collected data from the Nationwide Inpatient Sample database in order to analyze potential risk factors for TCM. They identified that age, gender, tobacco or alcohol use, dyslipidemia, hypertension, and external stressors, such as physical or emotional stress, contributed to an increased risk in the development of TCM[29]. Age and gender appear to the be the strongest risk factors as Deshmukh *et al*[29] revealed that women over the age of fifty-five had 4.8 times higher odds of developing TCM when compared to younger women. This increased risk is likely due to decreased circulating levels of estrogen levels and resultant increased sympathetic drive as noted previously in the findings of Templin *et al*[14].

LIMTATIONS

Although iatrogenic medication-induced TCM is likely related to excessive catecholamine administration based on the case reports listed in Table 1, procedure-induced TCM appears to be an associated but rare complication. It is likely that the patients involved in Table 2 experienced an endogenous catecholamine surge that resulted in transient cardiac dysfunction. With the exception of Chen *et al*[20], the case reports in Table 2 did not involve pre-procedural catecholamine administration; however, all patients experienced post-procedural TCM. Case reports listed in Table 2 did not elucidate on potential complications during procedures, such as transient hypotension or the administration of vasopressor support resulting in a catecholamine surge causing iatrogenic TCM. In addition, case reports did not consistently include their home medications. Withdrawal of certain medications could theoretically precipitate a catecholamine surge (*i.e.,* clonidine[30]) or render the patient more susceptible to the endogenous effects of catecholamines.

CONCLUSION

Although Takotsubo cardiomyopathy was first described in 1991, this specific type of cardiomyopathy has only recently gained increased recognition throughout the medical community. TCM is largely provoked by extreme, acute physical or emotional distress but there are now several iatrogenic cases involving catecholamine administration and post-procedural complications highlighted in Table 1 and Table 2. There are many aspects of TCM that are still not completely understood; however, future research should increase our understanding of this disease. It is important to acknowledge this clinical syndrome and its association with medications and procedures in order to better predict complications and potentially prevent further iatrogenic cases of Takotsubo cardiomyopathy.

FOOTNOTES

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