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Review

Takotsubo Cardiomyopathy

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Abstract

Takotsubo cardiomyopathy (TCM), also known as stress-induced cardiomyopathy or "broken heart syndrome," is a transient cardiac condition characterized by acute left ventricular dysfunction, often triggered by emotional or physical stress. It mimics acute coronary syndrome (ACS) in its presentation, with symptoms such as chest pain, dyspnea, and electrocardiographic changes, but lacks significant coronary artery obstruction on angiography. The hallmark of TCM is regional wall-motion abnormalities of the left ventricle, typically involving apical ballooning. The underlying pathophysiology is not fully understood, but it is hypothesized to involve catecholamine surge-induced myocardial stunning, microvascular dysfunction, or direct myocyte injury. TCM predominantly affects postmenopausal women and has a generally favourable prognosis, with most patients recovering normal cardiac function within weeks. However, complications such as heart failure, arrhythmias, and cardiogenic shock can occur in severe cases. Diagnosis requires integration of clinical, imaging, and laboratory findings to differentiate TCM from other cardiac conditions. Echocardiography and cardiac magnetic resonance imaging (MRI) are critical for evaluating ventricular function and ruling out alternative diagnoses. Management is primarily supportive, focusing on symptom control, hemodynamic stabilization, and addressing potential triggers. Long-term outcomes are generally good, but recurrence is possible, emphasizing the need for continued research into prevention and pathophysiological mechanisms.

Keywords: Takotsubo cardiomyopathy, Causes, Types, Diagnosis, Treatment, Management.

INTRODUCTION

Takotsubo cardiomyopathy (TC) is defined by a temporary and reversible systolic abnormality of the left ventricle's apical area resembling myocardial infarction (MI) in the nonexistence of coronary artery disease

(CAD). This clinical entity was initially described approximately 25 years ago. The word "Takotsubo" is a container used by the Japanese to catch octopus, which has a circular bottom and narrow neck, which resembles the heart's condition in TC to a certain degree. There are various types of left ventricular (LV) function abnormalities within this disease. The prevalence is 1.0-2.5%, with most cases to occur in post-menopausal women. Many conditions have been linked to TC, like over-stimulation of the sympathetic system, microvascular and myocardial tissue metabolism abnormality, and coronary artery vasospasm. Despite frequently being underdiagnosed, complete understanding is needed to optimize the management of the disease. This review will briefly explain the main features of TC, including definition and management protocol.[1]

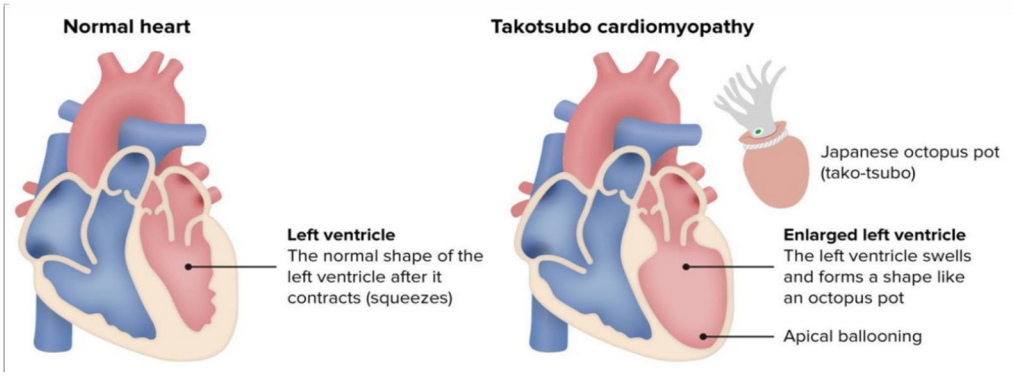

Fig 1: Takotsubo Cardiomyopathy

Takotsubo cardiomyopathy (TTC) is considered a mysterious and attractive entity described in Japan by Sato in 1990. The term this syndrome is derived from the Japanese word takotsubo (Tako means octopus; tsubo means pot) because the appearance of the left ventricle (LV) at the end of systole which can be visualized in trans-thoracic echocardiogram (TTE) or coronary angiography with left ventriculography is similar to a Japanese octopus fishing pot through the acute phase. TTC is a transient type of acute heart failure with distinct wall motion abnormalities. TTC has a significant economic burden on health care systems. In the US, the hospitalization rate due to TTC increased from 52 cases/million to 178 cases/million adult discharges over six years (i.e., six folds), with an annual nationwide cost burden exceeding 112$ million for the initial admission and readmission within 1-month. It was estimated that the average expenditure of care from hospitalization to six months after discharge was 11,491$ per patient. While the cost for the readmissions was equal to the entire cost of all outpatient and primary care coalesced.[2]

Subtypes

There are 4 subtypes of TTS defined by the distribution of wall motion abnormalities (Depicted in Figure 1 below). The InterTAK registry highlighted that the Apical Type was by far the most typical in TTS, but emphasised that other subtypes did exist. The subtypes described are:

1. Apical ballooning type (81.7%)
2. Mid ventricular wall motion pattern (14.6%)
3. Basal wall motion pattern (2.2%)
4. Focal wall motion pattern (1.5%).[3]

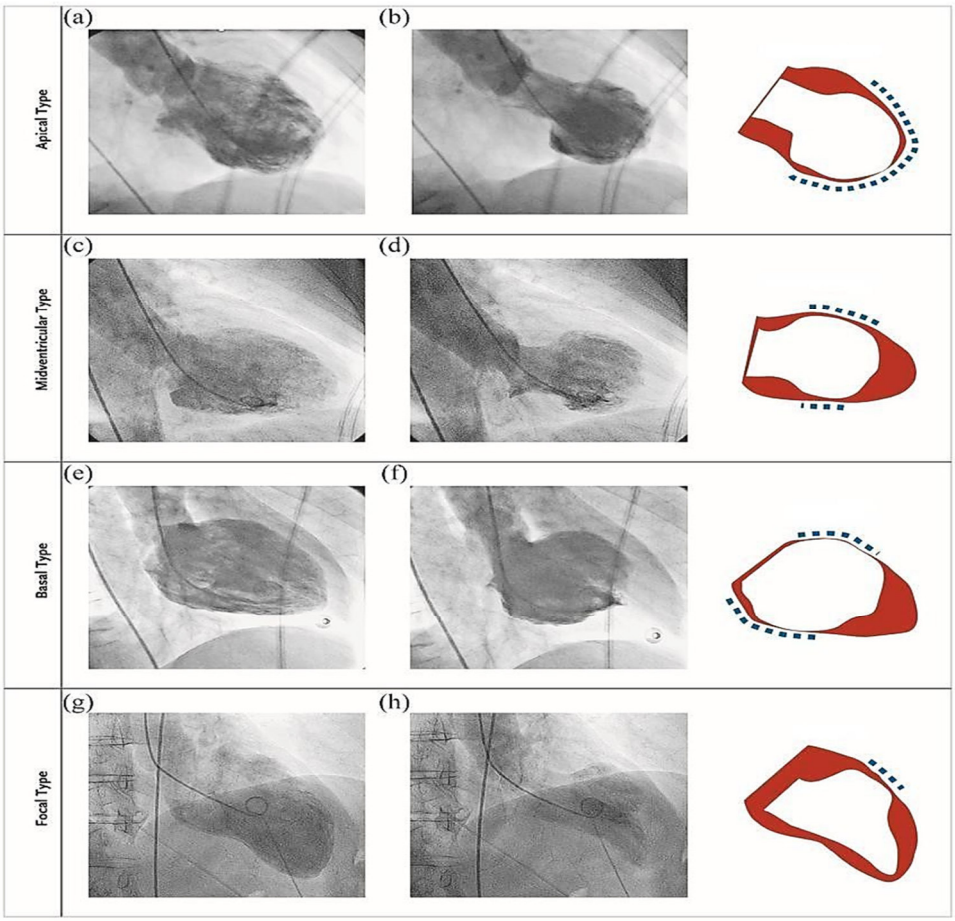

Fig 3: A depiction of the subtypes of Takotsubo syndrome shown during both diastole (left) and systole (middle). The right column depicts diastole in red and systole in white, with the blue lines representing the region of WMA.[3]

CAUSES AND TRIGGERS

Although the precise etiology of the syndrome is not known, the most plausible cause responsible for Takotsubo syndrome is the sudden release of stress hormones, such as norepinephrine, epinephrine, and dopamine, causing cardiac stunning. Stunning the heart triggers changes in the cardiac myocytes and coronary perfusion. Although roughly about one-fourth of patients have no clear triggers, Takotsubo syndrome is typically triggered by an unexpected emotionally or physically stressful event.

Events that have been reported to trigger TC include:

- Domestic abuse or relationship conflict
- Sudden loss of a loved one
- Natural disasters
- An accident or major trauma
- A fierce argument
- Severe financial or gambling losses
- An unexpected surprise like winning a lottery
- Being diagnosed with a serious acute medical condition or medical illness such as a stroke or a terminal illness
- Exhausting physical effort
- Surgery
- Head trauma
- Public speaking
- Extreme fright

- Use of drugs such as cocaine, excessive stimulant use, or inadvertent overdose of catecholamines
- Drug withdrawal.[4]

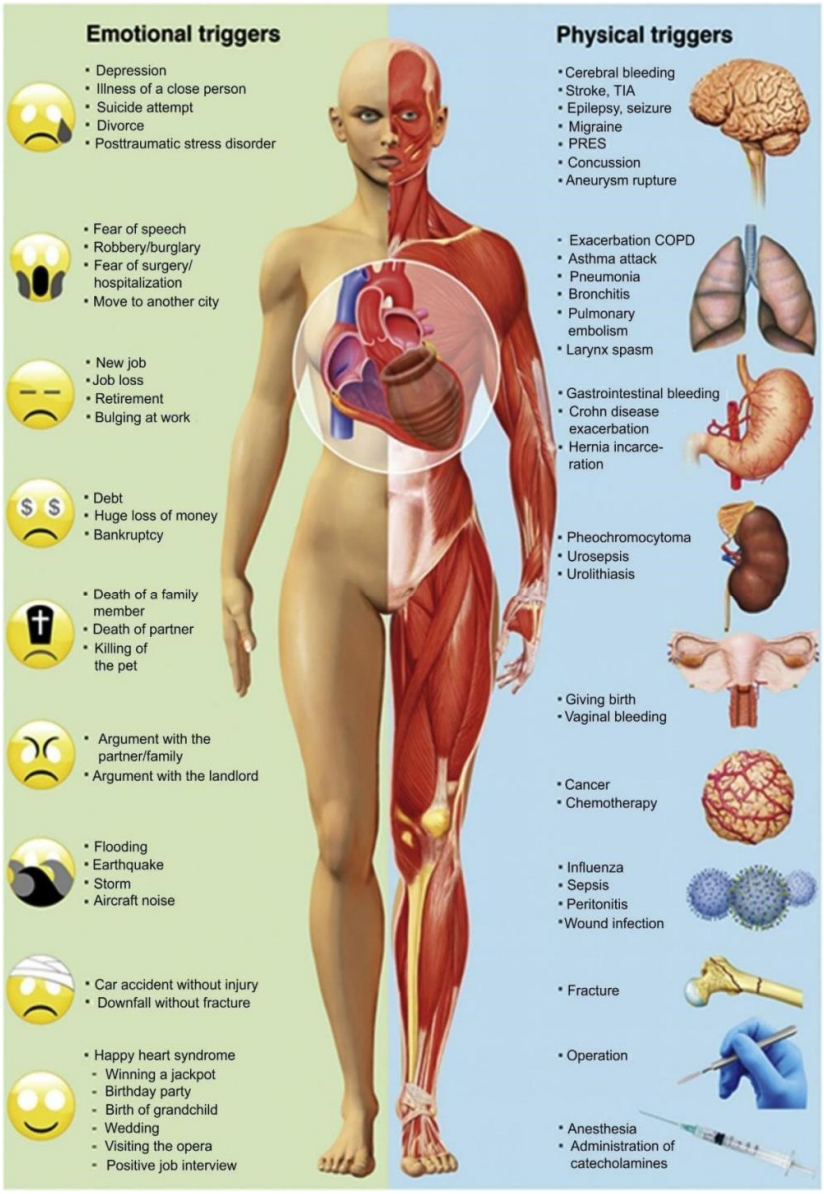

Fig 4: Examples of Primary (Emotional) and Secondary (Medical) Causes of Takotsubo Syndrome.[10]

Risk Factors

Despite encountering psychological and physical stressors frequently as a consequence of our daily life, TTS is relatively uncommon. As such it is hypothesised that there exist risk factors which render some people more susceptible to this condition than others.

Hormonal

The significantly increased prevalence of TTS in postmenopausal females suggests a potential role that declining oestrogen levels can play in increasing susceptibility in this group. In support of this theory is the noted 5-fold increased risk in women above the age of 55 compared with those younger than 55. It is known that oestrogen improves coronary blood flow at the coronary microcirculatory level 49 so oestrogen deprivation which leads to endothelial dysfunction may be implicated in the observed higher prevalence in postmenopausal women. However, the exact role of oestrogen in the development of TTS needs further investigation and clarification. Genetic Recent reports have described familial cases of TTS raising the possibility of a genetic predisposition

while others have described genetic heterogeneity implying a potential polygenic basis. In one study, inducible pluripotent stem cell derived cardiomyocytes (IPSC- CMs) from unrelated patients with a severe TTS phenotype demonstrated a strong and exaggerated catecholamine sensitivity associated with β-adrenergic signal alterations which suggested a genetic predisposition to catecholamine excess.

Psychiatric disorders

There is a strong association between pre-existing psychiatric illness and TTS, in particular anxiety, depression and chronic stress. When matched for age and sex, psychiatric and other neurological disorders were much higher in the TTS patients when compared to those with ACS.[5]

Diagnostic Evaluation

TTS can be difficult to diagnose as the clinical presentation is often similar to acute myocardial infarction. As such, TTS should be considered as a differential diagnosis in any patient presenting with chest pain and possible ACS, particularly when accompanied by a preceding intense emotional or physical stress or illness. Over the years, a number of diagnostic criteria have been developed, with the most recent being the Inter TAK Diagnostic Criteria developed by the Takotsubo International Registry[7]. The most significant changes from the preceding modified Mayo Clinic criteria acknowledges that significant coronary artery disease can co- exist with TTS and is not mutually exclusive, and that while an absence of pheochromocytoma was previously required, the InterTAK diagnostic criteria acknowledge that pheochromocytoma may function as a trigger for TTS. A diagnosis of TTS is more likely in institutions with primary percutaneous intervention (PCI) for ST elevation myocardial infarction and non-ST elevation myocardial infarction (NSTEMI) who undergo early invasive management. Therefore, a high index of suspicion is required for non-intervention facilities with first line fibrinolysis for STEMI; however, suspicion for TTS should not preclude administrating fibrinolytic therapy when indicated.[6]

INTERNATIONAL TAKOTSUBO DIAGNOSTIC CRITERIA (INTERTAK DIAGNOSTIC CRITERIA)[22]
1. Patients show transient[a] left ventricular dysfunction (hypokinesia, akinesia or dyskinesia) presenting as apical ballooning or midventricular, basal or focal wall motion abnormalities. Right ventricular involvement can be present. Besides these regional wall motion patterns, transitions between all types can exist. The regional wall motion abnormality usually extends beyond a single epicardial vascular distribution; however, rare cases can exist where the regional wall motion abnormality is present in the subtended myocardial territory of a single coronary artery (focal TTS).[b]
2. An emotional, physical or combined trigger can precede the takotsubo syndrome event, but this is not obligatory.
3. Neurologic disorders (eg, subarachnoid haemorrhage, stroke/transient ischaemic attack or seizures) as well as pheochromocytoma may serve as triggers for takotsubo syndrome.
4. New ECG abnormalities are present (ST-segment elevation, ST-segment depression, T-wave inversion and QTc prolongation); however, rare cases exist without any ECG changes.
5. Levels of cardiac biomarkers (troponin and creatine kinase) are moderately elevated in most cases; significant elevation of brain natriuretic peptide is common.
6. Significant coronary artery disease is not a contradiction in takotsubo syndrome.
7. Patients have no evidence of infectious myocarditis.[b]
8. Postmenopausal women are predominantly affected.

Investigations

Electrocardiogram

Electrocardiographic (ECG) should be performed in any patient with chest pain or suspicion of TTS. The priority should be identifying those patients who require urgent coronary angiography. Most patients with TTS have an abnormal ECG with ST-segment elevation and/or T-wave inversion. Similar to acute myocardial infarction the ECG in TTS can demonstrate localized and dynamic ischemic changes that evolve over time. ST-segment elevation was previously reported to be present in up to 80% of TTS cases, however this may be an overrepresentation as these patients are more likely to undergo diagnostic coronary angiography. Other features of myocardial infarction have also been noted, such as transient Q waves and flattening T waves with the return of prominence. The ECG may be unremarkable with non-specific changes noted. Regardless of ECG findings, the majority of patients will develop QT prolongation that normalize within 48hours. Q wave abnormalities typically resolve with restoration of normal R-wave progression before discharge from hospital while T-wave inversion may take longer if at all. One group has proposed an ECG criteria to distinguish TTS from acute myocardial infarction that includes absent abnormal Q waves, absent reciprocal changes, lack of ST-elevation in lead V1, and the presence of ST-elevation in AVR. The authors found these features to have a 91% Sensitivity and 96% specificity for TTS.

Coronary angiography

Coronary angiography has an important role in the diagnosis of TTS, in particular for those with ST-segment elevation. TTS is commonly diagnosed with coronary angiography and left ventriculography that shows akinesis of the mid and apical LV segments and hyperdynamic basal segments. Patients may have angiographically normal coronary arteries, or findings of atherosclerosis that is incongruent with the degree of LV dysfunction or regional wall-motion abnormalities demonstrated. In addition, invasive hemodynamic assessment can be used to assess for end-diastolic pressure (LVEDP), and the presence of a pressure-gradient in the outflow trac. Left ventricular outflow tract obstruction (LVOTO) is present in approximately 20% of patients with TTS and has implications for management. while LVEDP has been shown to be a good predictor of patients likely to have in-hospital complications.[7]

Echocardiography

Transthoracic echocardiography (TTE) is often the first imaging modality utilized in the acute phase of TTS and typically shows apical and mid ventricular wall motion abnormalities that appear akinetic or dyskinetic compared to the basal segments, giving the appearance of 'apical ballooning'. Typically, the wall motion abnormality is not limited to one arterial territory differentiating it from acute myocardial infarction. In the initial phase of TTS, LV function is reduced, however this dysfunction recovers with the resolution of myocardial stunning. Serial TTE is used in the recovery phase to monitor the improvement in LV function, with resolution seen on average by Day 18.

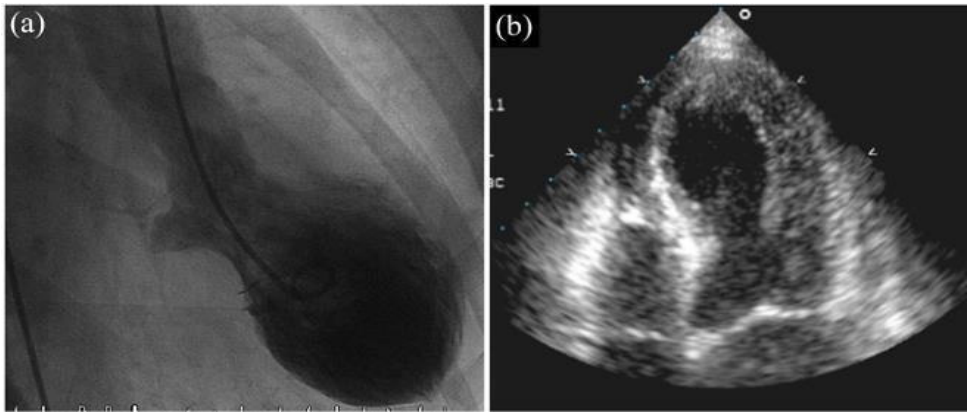

Fig 5: (a) Left ventriculogram right anterior oblique projection in end-systole demonstrating apical ballooning. (b) Four chamber transthoracic echocardiogram in end systole demonstrating apical ballooning. The area around the apex shows akinesis, and the basal segments display hypercontraction.

Cardiac computed tomography angiography

TTS is associated with several triggers such as intracranial bleeding, terminal malignancy and septic shock where invasive coronary angiography may not be appropriate. In these cases, and those with low suspicion of ACS, previous TTS and established coronary anatomy on prior recent angiography, computed tomography coronary angiography (CTCA) may be more appropriate.

Cardiac magnetic resonance imaging (CMR)

CMR imaging has been previously used in those with atypical features, bystander coronary artery disease or when there is suspicion for myocarditis. There is emerging evidence that routine use, particularly in the acute phase, assists in confirming the diagnosis, as well as identification of complications not evident on other imaging modalities. In the acute phase, reversible myocardial inflammation and oedema are hallmark findings of TTS and can be readily assessed with CMR through the utilization of T2-weighted sequences. In TTS, myocardial oedema is typical transmural and has been shown to resolve in six months. In the sub-acute phase, identifying subtle RWMAs makes CMR the ideal modality to accurately assess for resolution of regional dysfunction, with full-recovery being critical in con firming the diagnosis.[8]

Treatment

A correct diagnosis will avoid treatment of ischemic heart disease, which has not been shown to be of any bene f it in TS and could give rise to adverse effects. At the present time, treatment is symptomatic and, as with other cardiomyopathies, is determined by the complications occurring during the acute phase. The use of intra-aortic balloon pump (IABP) support has been required, and even cardiopulmonary support techniques and

renal replacement therapy such as continuous Veno venous hemodiafiltration. The use of inotropes is controversial due to the increase in circulating catecholamines. Levosimendan may be beneficial for its inotropic and vasodilator effects. IABP is re quired by 8–46% of patients, less than in the ACS. Up to 36.36% of patients require vasoactive drugs, and inotropes are used in 20–43.75%. Short-term anticoagulation may be considered, at least until recovery of ventricular function. The implantation of defibrillators is controversial; they are implanted in 2.5–8.3% of cases, but the number of arrhythmogenic events registered after a year of follow-up could be zero.

In the case of left ventricular outflow obstruction with hemodynamic repercussion, treatment should be given with beta-blockers, alpha-adrenergic agents such as phenylephrine, and volume expansion; calcium channel blockers may be used to reduce the outflow gradient. Most important in these cases is to treat the trigger and to recognize the condition in order to avoid treatment with nitrites or inotropes. The use of calcium channel blockers such as diltiazem or verapamil may be indicated if vasospasm is suspected. In the case of functional mitral insufficiency, initial treatment may be conservative; 36% require IABP and valve replacement may even be necessary. Long-term treatment is currently undefined. It is thought that it may be appropriate in order to reduce myocardial stunning caused by catecholamines and that it would theoretically avoid recurrences. However, there is no evidence to support the use of chronic pharmacological treatment except in cases of cardiac dysfunction, despite the fact that treatment could alter the incidence of recurrence. Experimental studies are evaluating the controversial benefit of estradiol, ranolazine, and the reduction in the frequency of recurrence through the administration of beta-blockers, but beta-blocking drugs were not absolutely protective.[9]

Critical Care Medicine and Takotsubo Syndrome

In 28% of cases, the apical ballooning syndrome develops in critically ill patients with no primary heart disease, but there are few studies on this subject due to a lack of diagnosis. The situation of stress to which the critically ill patient is subjected acts as a trigger. we studied 92 patients admitted to an intensive care unit and, through the use of echocardiography at the time of admission, with repetition a few days later, observed that 28% of patients presented echocardiographic abnormalities compatible with TS, with a reduction of the LVEF, and sepsis as the variable associated with cardiac dysfunction. This phenomenon has also been observed in critically ill patients with other diseases and even after cardiopulmonary resuscitation; these patients present echocardiographic signs of myocardial dysfunction, with an initially reduced LVEF that improves over time, as do the electro cardio graphic disturbances. It included 6 patients with a diagnosis of TS. All the patients presented electrocardiographic and echocardiographic disturbances with an initially reduced LVEF and normal angiography. The true prevalence is unknown. The age is similar to that of patients outside intensive care units (63–68 years). Only 35–50% are women. Clinically, the typical symptoms are not usually present, possibly due to the state of sedation-analgesia under which these patients are usually maintained, or due to the hemodynamic situation or severity of the critically ill patients. Occasionally patients refer pre cordial discomfort, although they are more likely to present pulmonary edema, ischemic changes on the ECG, sometimes detected by telemetry, arrhythmias such as ventricular tachycardia, a moderate rise in the biomarkers, or hemodynamic disturbances. The most prevalent risk factor is systemic hypertension. The echocardiographic, electrocardiographic, and enzyme changes normalise over a period that varies between 1 and 6 months. Mortality is somewhat lower: 67–52%, with higher figures than in patients not admitted to these units; the cardiac dysfunction possibly affects the prognosis. There is a growing need for vasoactive drugs: 54.55–83.33%. The etiology and pathogenesis are believed to be similar to other forms of TS.

The differential diagnosis must be made with stress cardio myopathies (of the critically ill patient, catecholamine-induced, neurological, and various respiratory insufficiencies). The cardiac dysfunction that develops could be an expression of a previous disease or the intercurrent situation that the patient is suffering, or procedures that the patient requires during admission to the intensive care unit (endotracheal intubation, mechanical ventilation, tracheostomy, etc), and not a true TS. The problem is in differentiating whether the disorder is due to the patient's underlying disease, is a TS, or if the 2 are the same thing. The end result is that the association with cardiac dysfunction can worsen the prognosis. Clinically, the subtlety of the initial symptoms, the lack of suspicion, and the low level of use of bedside echocardiography, means that diagnosis will be delayed and that treatments may be used erroneously and, on occasions, even with a risk of causing harm.[10]

Prognosis And Recurrence

Complications are estimated to occur in 18.9% of cases of TS, with no racial differences. Mortality varies between 0% and 12%. There are no long-term studies that provide approximate figures. He estimates in-hospital mortality at 1%, and mortality at 1 year of follow-up that reaches 2%. He observed that older patients die earlier and that whites had a higher mortality than Asians (6% vs. 1.7%). Parodi detected a higher mortality among coronary patients (14% vs. 3%). Nuñez-Gil did not observe any in-hospital deaths, but they did detect a mortality of 3.2% during follow-up (35 months), although these figures are lower than for ACS (hospital mortality: 6.5%; mortality during follow-up for 35 months: 17.2%). Other authors have not analysed mortality

in their studies. Morbidity and mortality are lower in TS patients than in patients with ACS, and left ventricular function could determine the prognosis. Recurrence is rare but has been reported. Clinically, the syndrome reappears as precordial pain and, morphologically, can vary in the type of echocardiographic or ventriculographic presentation. The time to recurrence varies between 3 months and 13 years. The incidence does not exceed 13% and, as a rule, recurrence is not observed. There is also doubt about whether all recurrences are TS. At the present time, reasonable doubt may still be expressed about the complete reversibility of a stress cardiomyopathy.[11]

Management

There are no specific treatments for the left ventricular failure characterizing takotsubo cardiomyopathy because cardiac function is normalized within a few weeks. When shock occurs, intra-aortic balloon pumping is established as additional support for the circulation. We use upright posture, oxygen, and diuretics for pulmonary edema, although given the putative pathophysiological mechanism, it would be reasonable to treat pulmonary edema with sedation and morphine. Arrhythmia resulting from QT prolongation is commonly observed in patients with takotsubo cardiomyopathy; however, we do not administer antiarrhythmics prophylactically. In our experience, administration of magnesium sulphate is effective for ventricular tachycardia in the acute phase of takotsubo cardiomyopathy if the QT interval is prolonged. We also do not administer-adrenoceptor blockers, which can prolong the QT interval and leave unopposed the potentially adverse effects of high local concentrations of catechol amines at-adrenoceptors. The use of-adrenoceptor blockers in the acute phase of takotsubo cardiomyopathy is still a matter of debate. Given the findings in the animal model, treatment with a combined- and-blocker seems rational, whereas treatment with a catecholamine as a cardiotonic seems contraindicated.

It should be kept in mind that Adrenalin (Parke-Davis & Co, Detroit, Mich) was originally marketed as a hemostatic agent, not a pressor or cardiotonic. We often encounter thrombosis in takotsubo cardiomyopathy cases, which might reflect vasoconstrictor, platelet activation, or prothrombotic effects of extremely high epinephrine levels. Because apical ballooning increases the risk of cardiac rupture, it is still controversial whether treatment with aspirin or heparin is indicated. The fact that epinephrine promotes platelet activation by stimulating platelet 2 adrenoreceptors provides additional rationale for treatment with a combined- and-blocker.[12]

CONCLUSION

Takotsubo Cardiomyopathy (TCM), or stress-induced cardiomyopathy, is a transient but significant cardiac condition that mimics acute coronary syndromes (ACS) in presentation but differs in etiology and prognosis. It is characterized by reversible left ventricular dysfunction, often triggered by physical or emotional stress, and predominantly affects postmenopausal women. The pathophysiology of TCM involves a complex interplay of catecholamine surge, myocardial stunning, and microvascular dysfunction, though it remains incompletely understood. Advances in diagnostic tools such as echocardiography, cardiac MRI, and coronary angiography have improved the identification and differentiation of TCM from other cardiac conditions. Management is largely supportive, with a focus on addressing hemodynamic instability, treating complications, and mitigating stressors. While the prognosis is generally favourable, severe complications like heart failure, arrhythmias, and recurrence may occur, warranting close monitoring and follow-up. Further research is needed to clarify the underlying mechanisms, identify high-risk populations, and develop preventive strategies. By improving our understanding of this unique condition, clinicians can enhance patient outcomes and provide more personalized care for those affected by Takotsubo Cardiomyopathy.

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