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Epidemiology, Pathophysiology, Diagnosis, and Principles of Management of Takotsubo Cardiomyopathy: A Review

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Takotsubo cardiomyopathy, also known as stress-induced cardiomyopathy, is a reversible syndrome commonly found among patients presenting for acute coronary syndromes, especially women. With the COVID-19 pandemic, the incidence of takotsubo cardiomyopathy was dramatically increased. However, this clinical cardiac entity remains underdiagnosed, largely due to the interplay with acute coronary syndrome. The pathophysiology of takotsubo cardiomyopathy is miscellaneous, including coronary vasospasm, microcirculatory dysfunction, catecholamine surge, and sympathetic overdrive. Diagnosing takotsubo cardiomyopathy requires a high index of clinical suspicion and multimodality tests. To date, there are no guidelines for the management of takotsubo cardiomyopathy. Thus, available data are derived from case series, retrospective analyses, and experts' opinions. Heart failure medicines were investigated in takotsubo cardiomyopathy patients. Evidence supports the benefits of angiotensin-converting enzyme inhibitors and angiotensin receptors blockers use on mortality and recurrence rates, while results from use of beta-blockers are controversial. In complicated cases, inotropes are preferred over vasopressors, except in the presence of left ventricular outflow tract obstruction, in which medical therapy is limited to fluids administration and beta-blockers. Use of oral vitamin K antagonist can benefit patients at high thrombo-embolic risk for up to 3 months. Mechanical supports are reserved for refractory hemodynamically unstable cases. This review aims to provide an update on the epidemiology, diagnosis, and outcomes of takotsubo cardiomyopathy, and an extended discussion on the management of complicated and non-complicated cases.

Keywords: Clinical Trial • Case Management • Takotsubo Cardiomyopathy

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Background

Numerous terms like "broken heart syndrome", "stress-induced cardiomyopathy", and "apical ballooning syndrome" have been used to describe takotsubo cardiomyopathy [1]. Takotsubo cardiomyopathy is a reversible acute cardiac condition related to transient regional left ventricular wall motion abnormalities extending beyond a single epicardial coronary artery territory [2]. It usually mimics acute coronary syndrome, and early coronary angiography is generally performed [3]. Due to this overlap between the initial clinical presentation of takotsubo cardiomyopathy and acute coronary syndrome, the Inter Tak Diagnostic Score has been recently developed to discriminate these 2 different entities in the acute stage [4]. Then, according to this score and, unlike the modified Mayo Clinic diagnostic criteria, the presence of significant coronary artery disease does not exclude takotsubo cardiomyopathy diagnosis. Four major patterns or variants of takotsubo cardiomyopathy are described in the literature: the apical ballooning form (typical form), accounting for 80% of takotsubo cardiomyopathy cases with the classical Japanese octopus trap feature [5]; mid-ventricular form with Hawk's beak appearance [6,7]; and basal and focal forms [1,8]. Formerly considered a benign self-limiting state, takotsubo cardiomyopathy is now known to be related to short- and long-term adverse cardiovascular outcomes [9-11]. Male sex, advanced age, reduced left ventricular ejection fraction below 35% at initial presentation, prolonged QT interval on electrocardiogram, identification of a physical trigger, atrial fibrillation, and development of acute complications are predictors of poor prognosis [2]. Management of takotsubo cardiomyopathy is based on anecdotal evidence from experts' opinions and case series, largely due to the absence of randomized clinical trials [12,13]. With the era of COVID-19 and the increased number of takotsubo cardiomyopathy cases, this review provides an update and short discussion about the epidemiology, pathophysiology, and diagnostic tests, and an extended discussion about the management of complicated and non-complicated cases based on the previously published expert consensus [12], recent reviews [13], and available studies. We also suggest a stepwise approach to the management of takotsubo cardiomyopathy. Physicians must deal with the underlying trigger when present, clinical cardiac manifestations, acute complications, and long-term recurrence risk. In general, heart failure medications are conventionally used in the setting of stress-induced cardiomyopathy. Herein, we review the management of and therapeutic approaches for takotsubo cardiomyopathy during the acute phase to call attention to the potential associated complications and to promote physician awareness, recognition, and care of this rare process. Therefore, this review aims to provide an update on the epidemiology, pathophysiology, diagnosis, management, and outcomes of takotsubo cardiomyopathy, also known as stress-induced cardiomyopathy.

Epidemiology

Takotsubo cardiomyopathy accounts 1% to 3% of acute coronary syndrome [1] and 0.5% to 0.9% of ST-segment elevation myocardial infarction [12]. It occurs predominantly in women, particularly in the post-menopausal period [13]. Women over 50 years old account for 80% to 90% of patients who develop takotsubo cardiomyopathy [2,14,15]. Takotsubo cardiomyopathy is usually underdiagnosed, especially in patients who have co-existing coronary artery disease, largely due to the interplay between acute coronary syndrome and takotsubo cardiomyopathy [16]. Precipitating physical or emotional or mixed stressful events have been identified in two-thirds of takotsubo cardiomyopathy cases [17]. The incidence of takotsubo cardiomyopathy has dramatically increased during the COVID-19 pandemic in association with psychological stressors such as social isolation, financial issues, and anxiety [18,19]. Moreover, takotsubo cardiomyopathy has also been reported as a rare complication after administration of novel messenger-RNA COVID-19 vaccines [20,21].

Pathophysiology

Although described 30 years ago, the exact pathophysiological mechanism of takotsubo cardiomyopathy remains unclear. Its pathophysiology varies, including coronary vasospasm, microcirculatory dysfunction, catecholamine surge, and sympathetic overdrive [22-24]. During the acute phase, the massive direct release of catecholamine by the sympathetic nerve endings into myocardium results in ventricular dysfunction and myocardial contraction band necrosis, a hallmark histological finding of takotsubo cardiomyopathy [25-27]. Some authors have suggested that this local catecholamine excess dysregulates myocardial calcium-handling and has more cardiotoxic effects than the circulating one [28,29]. This local catecholamine overexpression may also explain why the catecholamine bloodstream level is not always elevated. The difference in the distribution of β1 and β2 adrenoreceptors densities between the apical and basal cardiac segments could explain the observed left ventricular contraction abnormalities in the apical ballooning variant of takotsubo cardiomyopathy [28,30]. Apart from the most established adrenergic hypothesis, it is still debated whether coronary microvascular dysfunction is a consequence of or the primary cause of acute episodes of takotsubo cardiomyopathy. Repeated provocation tests showed reproducible coronary vasospasm in 20% of takotsubo cardiomyopathy patients [31].

Diagnostic Investigations in Takotsubo Cardiomyopathy

Electrocardiogram is the primary diagnostic test performed after the first medical contact with takotsubo cardiomyopathy

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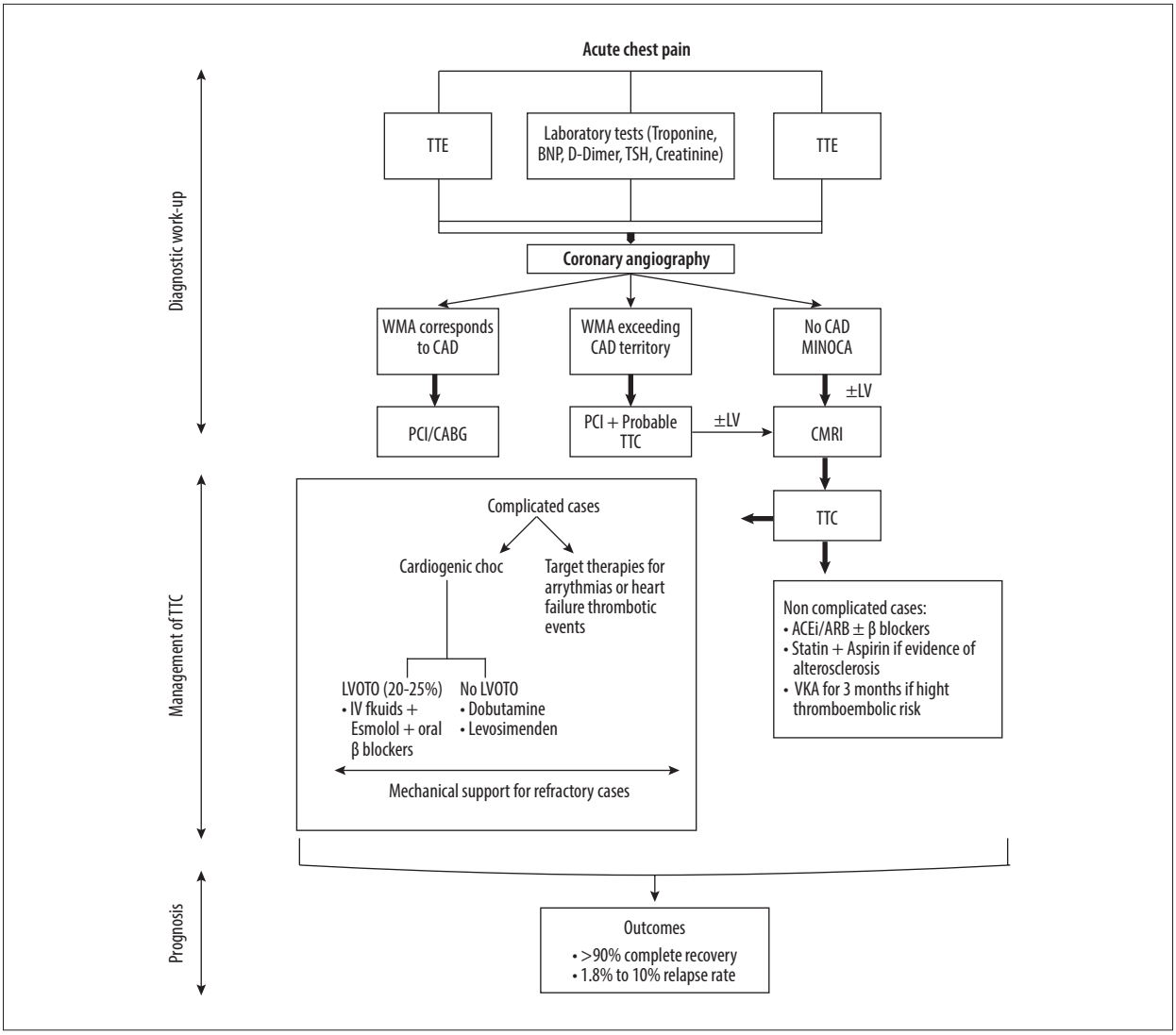

Figure 1. Stepwise approach of the management of takotsubo cardiomyopathy. ECG – electrocardiogram; TTE – transthoracic echocardiography; WMA – wall motion abnormalities; CAD – coronary artery disease; MINOCA – myocardial infarction with non-obstructive coronary arteries; PCI – percutaneous coronary intervention;CABG – coronary artery bypass graft; CMRI – cardiac magnetic resonance imaging; ACEi – angiotensin-converting enzyme inhibitors; ARB – angiotensin receptor blockers; VKA – vitamin K antagonist.

patients, who commonly present with acute-onset chest pain and/or dyspnea mimicking acute coronary syndrome. Electrocardiogram reveals persistent or dynamic ischemic changes like ST-segment elevation, ST depression, prolonged QT interval, and T wave inversion [32,33]. ECG changes are usually not localized to a particular territory and progress over 3 stages [34-36]. The stage 1 is marked by ST-segment deviation in the early hours of symptoms onset, stage 2 involves T wave inversion and QT interval prolongation occurring within the first 72 hours, and stage 3 is characterized by gradual regression of abnormalities over weeks or months. Systematic transthoracic echocardiography has several advantages: it delineates ventricular wall motion abnormalities, evaluates left ventricular ejection fraction, and assesses acute complications (thrombus formation, mitral regurgitation, ventricular rupture, and left ventricular outflow tract obstruction) [37-39]. Almost all takotsubo cardiomyopathy patients undergo coronary angiography, that reveals normal or nearly normal coronary arteries or obstructive coronary artery disease incongruent with myocardial kinetic abnormalities [13]. Co-existing coronary artery disease is reported in 15% of takotsubo cardiomyopathy cases [40,41]. The diagnostic investigation tests routinely end with cardiac magnetic resonance imaging with gadolinium contrast administration, which helps to exclude other differential diagnoses or pathologic states (eg, acute myocardial infarction and myocarditis), and identifies the potential complications (eg,

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thrombi formation, right ventricle involvement, and pericardial and pleural effusion) [2,13]. Myocardial edema is the principal cardiac magnetic resonance feature of takotsubo cardiomyopathy. Levels of cardiac biomarkers (BNP/NT-pro BNP and troponin T) are generally increased in a disproportion way. A large increase in BNP/NT-pro BNP level is associated with a slight rise in troponin T concentration, and this discrepancy can help differentiate takotsubo cardiomyopathy from acute myocardial infarction in the acute presentation. Indeed, high NT-pro BNP/troponin T ratio is suggestive of takotsubo cardiomyopathy, with a sensitivity of 91% and specificity of 95% [42].

General Management of Non-Complicated TTC (Figure 1)

Till now, there are no guidelines for the management of TTC, and heart failure medications have been investigated in different retrospective analyses. The cardiovascular outcome of antithrombotic therapy remains debatable, especially in the absence of obstructive CAD. First, the use of ACEi (angiotensin-converting enzyme inhibitors) or ARB (angiotensin receptor blockers) has proved positive effects on 1-year survival in TTC patients [43] and reducing TTC recurrence risk [44,45]. Second, no beneficial effects for beta-blockers against mortality and recurrence rate have been observed [41-46]. However, recent studies described long-term (up to 3-years) improvement in left ventricular systolic function [47] and reduction of cardiovascular mortality [48] in conjunction with beta-blockers use. Lastly, standard heart failure treatment combining beta-blockers and ACEi or ARBs with or without aspirin and statin has revealed controversial results. While numerous studies have reported favorable result with this combination [49-51], no reduction in TTC recurrence at 3-year follow-up and an absence of significant improvement in left ventricular function and duration of hospital stay have been revealed by others [52-54]. Interestingly, the reported rate of recurrence of TTC is low [48]. Focusing on antithrombotic therapy, the early use of low-molecular-weight heparin in the acute phase followed at hospital discharge by up to 3 months of oral anticoagulant treatment has benefits in stroke prevention, especially in patients at high thromboembolic risk [55,56]. Although aspirin or dual antiplatelet (aspirin + clopidogrel) intake may reduce the major cardiovascular events including stroke [48], a recent study conducted on 1553 TTC patients found no effects of aspirin use on prognosis and complications development [57]. Thus, statins and aspirin are conventionally recommended in the setting of co-existing CAD [2]. A fast reduction in inflammatory biomarkers was associated with 600 mg daily use of alpha-lipoic acid [58]. In general, the optimal duration of TTC treatment ranges from 3 months to 1 year, depending on cardiac function recovery [59]. There are 2 ongoing prospective randomized clinical trials. The first, NACRAM trial, is investigating the benefits of early intravenous administration of n-acetylcysteine followed by oral ramipril for 3 months on myocardial edema reduction and cardiac function improvement [60]. The second, an interventional trial, is evaluating outcomes of early TTC patient rehabilitation [61]. The advantages of hormone therapy (estrogens) in the long-term management of TTC are still being studied. Angiotensin-neprilysin receptor inhibitors, SGLT2 inhibitors, and mineralocorticoid receptor antagonists, which are recommended in the context of heart failure, have not tested in TTC patients to date. Physicians must also deal with precipitating triggers when present, such as psychiatrist referral and antidepressant prescription. To summarize, the available evidence supports the use of ACEi or ARB in hemodynamically stable uncomplicated cases of TTC. The outcomes from the use of all other pharmacological agents remain unclear.

Management of Complicated TTC

TTC may lead to serious life-threatening complications like acute heart failure (HF), cardiac rupture, cardiogenic shock, thromboembolic events, and arrhythmias.

Acute Heart Failure

The management of acute HF after TTC is driven by the standard international guidelines for HF, comprising oxygen and respiratory support, ACEi, ARB, ARNI, beta-blockers, mineralocorticoid receptors antagonist, and diuretics. Thus, the only difference is to avoid pharmacological therapies for preload and afterload reduction in the setting of left ventricular outflow tract obstruction (LVOTO). While beta-blockers did not show an effect on survival in HF-TTC patients [46], they showed a reduction of cardiac rupture incidence [62]. The average duration of medical treatment is up to 4 weeks.

Cardiogenic Shock

Within the first 72 hours of hospital admission for TTC, cardiogenic shock occurs in 11% of hospitalized patients, and 20% to 25% present with left ventricular outflow tract obstruction (LVOTO) [63]. Positive inotropic agents (eg, dopamine/dobutamine) are preferred over sympathomimetic cholinergic vasopressors (eg, ephedrine/norepinephrine) to restore cardiac function and blood pressure. Exacerbated in-hospital and long-term mortality rates have been observed with catecholamine administration for circulatory support in hemodynamically unstable TTC patients [64]. Mechanical support is considered for refractory and/or severe cases with and without LVOTO. However, it is mandatory to check for LVOTO before initiating therapy, as this condition contraindicates inotropic drugs and intra-aortic balloon pump. In case of LVOTO, the first medical treatment is limited to fluid resuscitation and beta-blockers. Santoro et

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al revealed the efficacy of early intravenous administration of esmolol followed by daily bisoprolol in decreasing LVOTO gradient and alleviating obstruction [65]. Intravenous injection of levosimendan, a calcium-sensitizing agent and ATP-potassium channel-opening mediator, significantly improves left ventricular function in the setting of TTC-cardiogenic shock [66].

Thromboembolic Events

Left ventricular thrombus formation and subsequent systemic embolization occur in 1$ to 2% of TTC cases, especially in those with severely altered left ventricular systolic function. When left ventricular thrombus is detected either by transthoracic echocardiography or cardiac MRI, oral anticoagulation therapy based on vitamin K antagonist is recommended for at least 3 months to prevent thrombus migration [55]. The efficacy of novel non-vitamin K oral anticoagulant has not been studied in TTC.

Arrhythmias

Ventricular tachycardia or ventricular fibrillation represents two-thirds of TTC-associated arrhythmia [67,68]. Closed QT interval and telemetry monitoring during the acute phase were suggested. Intravenous magnesium is the first therapeutic approach for torsade de pointes, followed by isoproterenol for non-responders. Amiodarone is the preferred anti-arrhythmic drug compared to other drugs that may also prolonged QT interval. Finally, the question concerning permanent pacemaker or defibrillator implantation versus temporary device use in case of severe arrhythmias (high-grade atrio-ventricular block, ventricular arrhythmias) is still debatable [59].

Takotsubo Cardiomyopathy Patient Outcomes

The overall prognosis of TTC is favorable with complete recovery in more than 90% of patients within 1-2 months. However, the reported prevalence of relapse ranges from 1.8% to 10% [43,45,69,70]. Women with advanced age (›50 years), severely altered left cardiac function, vulnerability to emotional stress, and fluctuations in cardiac baroreceptors were identified as independent predictors of recurrence [71]. In addition, male sex, high-grade Killip on hospital admission, and diabetes mellitus were recognized as independent predictors of mortality [72]. A recently published study showed lower mortality and recurrence rates at 5.2-year follow-up in TTC patients treated with beta-blockers only compared to those receiving ACEi or ARB alone [70]. Finally, modifying lifestyle by reducing caffeine consumption and smoking cessation help to prevent TTC recurrence [73].

Conclusions

To summarize, diagnosing TTC requires a high index of clinical suspicion and multimodality tests. The management of TTC is personalized care analyzed on a case-by-case basis. A primary diagnostic work-up is essential to screen for the presence of potential complications, especially for LVOTO, which may drive the therapeutic approach. ACEi/ARB and beta-blockers are commonly used in non-complicated patients, while mechanical supports, vasopressors, and inotropes are reserved for severe cases. Statins and aspirin are advised if atherosclerotic signs co-exist. Long-term management includes screening for triggers or precipitant factors, monitoring for recurrence, and cardiac rehabilitation. Further prospective randomized clinical trials are warranted to establish standard guidelines.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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