Chapter 11

The Clinical Manifestations, Diagnosis and Management of Takotsubo Syndrome

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http://dx.doi.org/10.5772/68037

Abstract

The Takotsubo syndrome (TTS) is a transient cardiac dysfunction characterised by a variety of ventricular wall-motion abnormalities. Alternative nomenclatures for this disorder include stress-induced cardiomyopathy, apical ballooning syndrome and 'broken heart syndrome'. TTS bears stark resemblance to an acute coronary syndrome, wherein patients present with acute chest pain and initial diagnostic workup correlates to abnormalities suggesting significant coronary stenosis. Interestingly, the distinguishing factor in TTS is the absence of an occlusive coronary vascular disease, which could correlate with these changes. The underlying pathophysiology explaining the evolution of TTS is still debatable; however, results from various recent studies and registers have shed more light on this obscure clinical entity. The detailed description of a criterion which demonstrably includes most patients with probable TTS has helped tune management strategies in ensuring necessary supportive care and early therapeutic interventions of complications, which could arise in course of the disease.

Keywords: Takotsubo cardiomyopathy, pathophysiology, catecholamines, complication, diagnosis, treatment

1. Introduction

The *Takotsubo* syndrome (TTS), first described in 1990 by Sato et al., is a transient cardiac dysfunction characterised by a variety of ventricular wall-motion abnormalities [1, 2]. Its name is derived from the resemblance of the left ventricle at end-systole to the octopus-pots of Japanese fishermen in the Hiroshima fish markets [3]; however, alternative nomenclatures such as stress or stress-induced cardiomyopathy, apical ballooning syndrome and 'broken heart syndrome' have also been used to label this usually reversible form of acute heart failure [4–7]. This clinical entity essentially mimics an acute coronary syndrome, wherein patients

present with acute chest pain, and demonstrates the typical biomarker profile (release of cardiac troponin and creatine kinase) and/or electrocardiographic abnormalities suggesting significant coronary stenosis. Interestingly, the distinguishing factor in Takotsubo syndrome is the absence of an occlusive coronary vascular disease, which correlates with these changes [8]. Although, the pathophysiology of this disorder remains unclear, recent hypotheses have suggested a form of acute catecholaminergic myocardial stunning to explain the pattern of temporary LV dysfunction and regional wall-motion abnormality commonly seen at the time of presentation [9].

2. Definition

The Takotsubo syndrome is an acute and usually reversible form of heart failure, precipitated by physical and/or emotional stresses or in some cases without any evident preceding trigger. In recent years, various institutions and working groups such as the Mayo Clinic, the Gothenburg group, the Japanese Circulation Society and the Takotsubo Italian Network have proposed their diagnostic criteria to better define this disease; however, in 2015, the Heart Failure Association for the European Society of Cardiology (HFA) outlined its conclusive version. This has been outlined in **Table 1** [8, 10]. A significant feature of this criterion is the inclusion of pheochromocytoma as a trigger for this syndrome. Patients diagnosed with this disorder could suffer from an acute Takotsubo syndrome in the event of a catecholamine storm, analogous to the response incited by other emotional or physical stresses.

- Transient regional wall-motion abnormalities of LV or RV myocardium which are frequently, but not always, preceded by a stressful trigger (emotional or physical).
- The regional wall-motion abnormalities usually[a] extend beyond a single epicardial vascular distribution, and often result in circumferential dysfunction of the ventricular segments involved.
- The absence of culprit atherosclerotic coronary artery disease 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, viral myocarditis).
- New and reversible electrocardiography (ECG) abnormalities (ST-segment elevation, ST depression, LBBB,[b] T-wave inversion, and/or QTc prolongation) during the acute phase (3 months).
- Significantly elevated serum natriuretic peptide (BNP or NT-proBNP) during the acute phase.
- 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]
- 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]Left bundle branch block 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 normalise after recovery of LV function.

[c]Troponin-negative cases have been reported, but are atypical.

dSmall apical infarcts have been reported. Bystander sub-endocardial infarcts have been reported, involving a small proportion of the acutely dysfunctional myocardium. These infarcts are insufficient to explain the acute regional wall-motion abnormality observed.

Table 1. Heart Failure Association diagnostic criteria for Takotsubo syndrome [10].

http://dx.doi.org/10.5772/68037

3. Clinical subtypes: the primary and secondary Takotsubo syndrome

An attempt to classify Takotsubo patients based on the evolving clinical scenario has helped outline two elemental subtypes. The primary form of the syndrome includes patients developing acute cardiac symptoms, possibly in the wake of a stressful trigger, as also those whose co-morbid conditions act as predisposing factors indirectly contributing to rising levels of catecholamines. The secondary form comprises patients, wherein the result is essentially a response to either a primary medical condition or treatment, and the pathophysiological process is probably mediated by a sudden activation of the sympathetic nervous system or at times by an increased catecholamine activity [11]. Some examples of triggers for the secondary Takotsubo syndrome include acute neuromuscular crises, especially if involving acute respiratory failure (acute myasthenia gravis, acute Guillain-Barre syndrome), attempted suicide, severe sepsis, infection, babesiosis, pacemaker implantation, electrical DC conversion for atrial fibrillation, acute pulmonary embolism, acute pneumothorax, pheochromocytoma, Addisonian crisis, hyperglycaemic hyperosmolar state, blood transfusions, thrombotic thrombocytopenic purpura, acute exacerbation of asthma or COPD, induction of general anaesthesia, cocaine abuse, acute cholecystitis, acute pancreatitis, surgery, dobutamine stress echocardiography, etc.

4. Anatomical variants

A study describing the varying morphological presentations of the left ventricle in patients diagnosed with the Takotsubo syndrome has led to the identification of at least four major anatomical variants [12, 13]. The classical pattern defined by an apical ballooning of the left ventricle at end-systole is present in at least 50–80% of the cases. The inverted Takotsubo (basal) variant with a predominantly hypokinetic circumferential base; the mid left ventricular variant with a hypokinetic circumferential mid ventricle; and the focal variant constitute other forms of presentation. Rarer variations include cases with a pronounced dysfunction of the biventricular apex and those with an isolated right ventricular involvement [14–16].

5. Epidemiology

A retrospective review of studies reporting cases of the Takotsubo syndrome has estimated that these patients account for approximately 2% of all suspected cases of an acute coronary syndrome [17]. The average age of the TTS patient at presentation was around 68 years and the gender bias skewed to a female preponderance for disease, with 90% of the diagnosed population constituting postmenopausal women. The Nationwide Inpatient Sample Database (NIS-USA) reported that 24,701 patients were diagnosed with the Takotsubo syndrome between 2008 and 2009 in the United States, and an extrapolation of this data suggests that there could be as many as 50,000–100,000 cases per annum in the United States alone [11].

6. Pathophysiology

There have been several hypotheses postulated in contemporary literature, insinuating the complex pathophysiological evolution of the Takotsubo syndrome from either possible coronary microvascular dysfunction, coronary artery spasm, catecholamine-induced myocardial stunning, acute left ventricular outflow obstruction, acute increased ventricular afterload, myocardial microinfarction or abnormalities in cardiac fatty acid metabolism [10]. The potential for excessive hypothalamic-pituitary-adrenal axis (HPA) gain and epinephrine release in the event of a stressful trigger, and the corresponding response of the cardiovascular system and the sympathetic nervous system to the following surge in levels of catecholamines is the driving theory currently attributed to the pathophysiological evolution of TTS [10, 18].

The consistent presence of microvascular dysfunction in TTS patients has been effectively elucidated in the studies by Uchida et al. (report of extensive endothelial cell apoptosis on myocardial biopsy) and Afonso et al. (demonstrated circulatory disturbance on myocardial contrast echocardiography). A detailed study describing coronary microvascular dysfunction in patients diagnosed with the Takotsubo syndrome suggested abnormalities consistent with endothelium-dependent vasodilation, excessive vasoconstriction and impairment of myocardial perfusion [19]. Additionally, myocardial biopsy of these patients showed regions with contraction band necrosis, inflammatory cell infiltration and localised fibrosis [20]. These changes have been attributed to direct catecholamine toxicity on cardiac muscle cells [21]. Kurisu et al. demonstrated using the TIMI frame count method, which impaired coronary blood flow corresponding to LV wall-motion abnormalities immediately after onset of TTS and improved on the resolution of the LV dysfunction, giving credence to the theory of coronary microvascular impairment.

In another study, Morel et al. suggested that an increase in C-reactive protein levels and white blood cell counts corresponded to increased levels of catecholamines in TTS patients [22]. The possible role of systemic inflammation mediated by catecholamine-induced pro-inflammatory cytokines like TNF-alpha and interleukin-6 has been used to explain the myocardial oedema observed in cardiac MRI [23].

Recent studies conducted by Wittstein et al. (proving catecholamine levels are two to three times greater in patients with TTS as compared to those with myocardial infarction) and Lyon et al. (proposing '*stimulus trafficking*' as the cause of decline of myocyte contractile function in TTS patients) give support to the theory that catecholamine-induced cardiotoxicity plays a significant role in the development of the Takotsubo syndrome [17]. It is currently hypothesised that the pathophysiology of TTS could be dictated by changes in beta-adrenergic receptor (AR) signalling [24–26]. A switch in intracellular signal trafficking from Gs protein to Gi protein (signalling through the β2AR) mediates a negative inotropic effect, greatest at the apical myocardium where the density of β-adrenoceptors is the highest. This mechanism of stimulus trafficking is triggered by excessively high levels of catecholamines and has been used to explain the acute apical cardio-depression in TTS [26].

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7. Risk factors

Lack of oestrogen has often been cited as a risk factor contributing to the development of TTS. The preponderance of postmenopausal women affected by this syndrome has led to studies investigating the use of hormone replacement theory among these patients. One such study by Kuo et al., although constituting a small sample size, showed that none of their TTS patients received any form of oestrogen replacement [27]. Recent work by Ueyema et al. in ovariectomised rats subjected to stress showed that decrease in LV function was more pronounced in those receiving estradiol supplements [28].

Patients with mood disorders and those using antidepressants tend to have an increased risk of developing TTS [29]. There is also an attempt to identify genetic factors that could suggest susceptibility to this syndrome. Although adrenoceptor polymorphisms are yet to be identified, patients with TTS have been shown to have a L41Q polymorphism of G protein coupled receptor kinase (GRK5) more frequently as compared to the normal population [30].

8. Clinical features of the Takotsubo syndrome

The definitive patient with a primary Takotsubo syndrome would be represented by a postmenopausal woman with experience of an acute, unexpected emotional or physical stress [31]. This bias, however, does not preclude men, younger women and patients with no identifiable trigger from a possible TTS. Consequently, gender, menopausal status and stressful triggers are not mandatory features included in the HFA criteria.

Patients typically present with acute chest pain are consistent with symptoms of angina pectoris, dyspnoea and palpitations. Pre-syncope and syncope due to ventricular tachyarrhythmia, severe left ventricular outflow tract obstruction and cardiogenic shock are more serious manifestations of this syndrome. Non-specific symptoms such as weakness, cough and fever have also been reported [32–34].

9. Diagnosis

9.1. Laboratory investigations

The measurement of cardiac enzymes such as serum troponin and creatinine kinase is essential to the diagnosis of the Takotsubo syndrome. Although, cardiac troponin levels are elevated in most patients with TTS, the rise in its levels is disproportionately low relative to the extent of regional wall-motion abnormality and cardiac dysfunction [24, 35]. In contrast, elevated values of cardiac natriuretic peptides, such as pro-BNP and NT-proBNP, serve as a better correlate for degree of ventricular wall dysfunction in the acute phase of TTS [36–38]. Normal values

of NT-proBNP are extremely rare in Takotsubo syndrome, thus helping it serve as a valuable marker of myocardial deterioration and recovery.

Recent studies have suggested the potential of circulating microRNAs to differentiate between TTS and STEMI patients; however, conclusive research is needed to establish this as a routine diagnostic biomarker [39].

9.2. Electrocardiography

The acute phase of TTS is characterised by ECG abnormalities such as ST-segment elevation, ST-segment depression, new left bundle branch block, Q-waves, T-wave inversions and significant QT-interval prolongation developing 24–48 hours after onset. These changes are reflected in almost 95% of all patients diagnosed with the Takotsubo syndrome [40]. It is not uncommon for the QTc-interval to be prolonged more than 500 ms, predisposing the patient to torsades de pointes and ventricular fibrillation, see **Figure 1**.

9.3. Echocardiography

The initial assessment of LV morphology and function with the use of thoracic echocardiography is inherent to the diagnostic cascade of Takotsubo syndrome. Standard, colour and tissue Doppler techniques assist in the identification of anatomical variants, monitor recovery and help detect potential complications such as left ventricular outflow tract obstructions, RV involvement, mitral regurgitation and cardiac rupture [41–43].

The echocardiographic examination of patient in the acute phase of TTS shows a large area of poorly functioning myocardium extending beyond the territory of a single coronary artery.

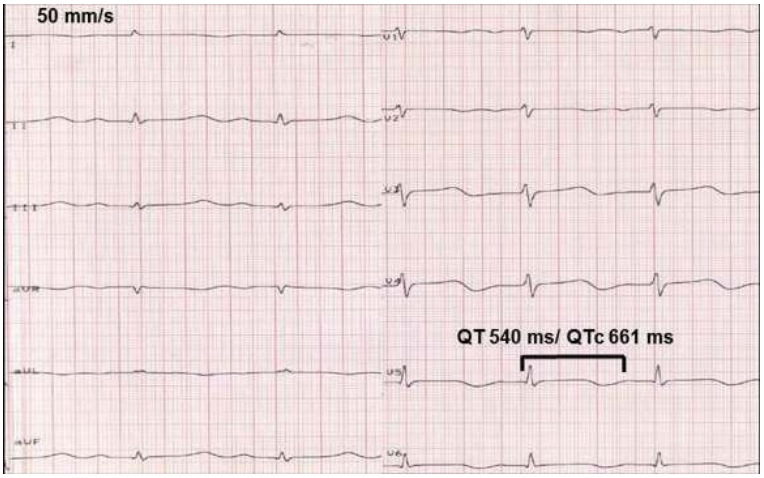

Figure 1. Electrocardiogram of TTS patient with acquired long QT syndrome at admission.

http://dx.doi.org/10.5772/68037

The typical regional wall-motion abnormality is found in the apical to mid segments of the left ventricle, extending equally into the anterior, inferior and lateral walls. This 'circumferential pattern' is considered the hallmark of TTS. In certain cases, the use of a contrast agent for LV opacification eases assessment of the RWMA, while, myocardial deformation imaging with the speckle tracking method has been used to demonstrate a transient circular impairment of not only longitudinal LV function, but also circumferential and radial LV function [44–46].

9.4. Cardiac magnetic resonance

The use of cardiac magnetic resonance imaging (CMR) has been advocated in the first 7 days (acute phase) to accurately assess both LV and RV regional function and demonstrate the typical patterns of RWMA, permitted by the full visualisation of the ventricles in the main long axes. Cardiac magnetic resonance imaging has a distinct advantage over standard transthoracic echocardiography in offering better views of the right ventricle and in detection of apical LV thrombi [47].

In CMR, tissue characterisation of acute myocardial changes occurring in the TTS patient shows a high signal intensity with a diffuse or transmural distribution, indicative of oedema of the hypokinetic LV myocardium. This oedema corresponds to the region of the wall-motion abnormality and is not restricted by the boundaries of a single coronary artery territory, unlike an acute myocardial infraction in which oedema is always coherent with a vascular distribution [42].

Late Gadolinium Enhancement (LGE) is typically absent in both the acute phase as well as follow-up, serving as an important criterion to distinguish between AMI and TTS. Recently, there has been some debate concerning the presence of minor LGE in the acute phase; however, this is dependent on the threshold of signal intensity used to define LGE presence [48, 49], see **Figure 2**.

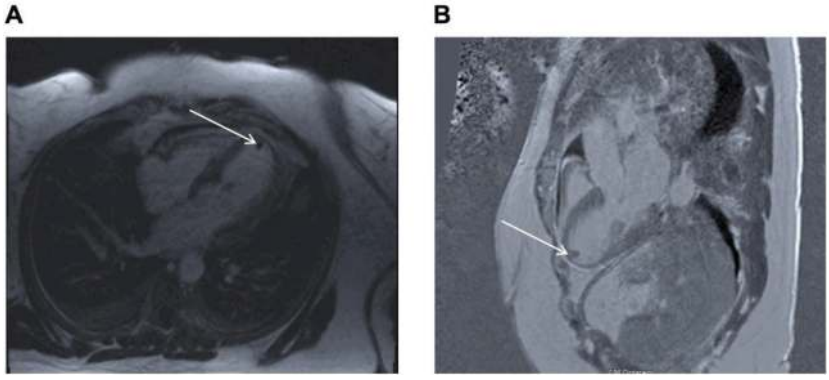

Figure 2. Magnetic resonance tomogram of patient with biventricular TTS showing a left ventricular thrombus formation as a related complication to TTS.

9.5. Coronary angiography and left ventriculography

The necessity to exclude an acute myocardial infarction in patients presenting with angina-like symptoms and typical ECG-changes predicates the use of coronary angiography. In TTS, the epicardial coronary arteries typically do not have any significant stenoses; however, there is possibility of bystander CAD considering the older age group of the presenting patients. A co-existing CAD has been reported in almost 10% of all TTS cases [50, 51]. The coronary stenosis in this scenario may or may not be hemodynamically significant; however, it is generally insufficient to explain the acute LV dysfunction and regional wall-motion abnormalities transpiring in the Takotsubo syndrome.

The exclusion of occlusive coronary artery disease, acute plaque rupture, thrombus formation and coronary dissection should be followed by a left ventriculography (if not contraindicated). This is necessary to confirm the pattern of LV wall-motion abnormality and diagnose, if any, mitral regurgitation. It also allows direct measurement of the pressure gradient across the LVOT [42], see **Figure 3**.

9.6. Coronary computed tomography angiography

The role of coronary computed tomography angiography (CCTA) is limited to cases where a delay in access to urgent invasive coronary angiography is expected. Information acquired throughout the cardiac cycle (spiral or helical acquisition mode) during the acute phase could demonstrate the typical pattern of systolic dysfunction [52]; however, this would come at the cost of greater radiation exposure. Retrospective evaluation of patients with typical history of TTS could also theoretically include CCTA to exclude significant coronary stenosis.

9.7. Radionuclide imaging

Single-photon emission tomography (SPECT) with ^{201}Thallium or ^{99m}Technetium-labelled radiopharmaceuticals and ^{123}I-metaIodobenzyl-guanidine (mIBG) has been used to demonstrate

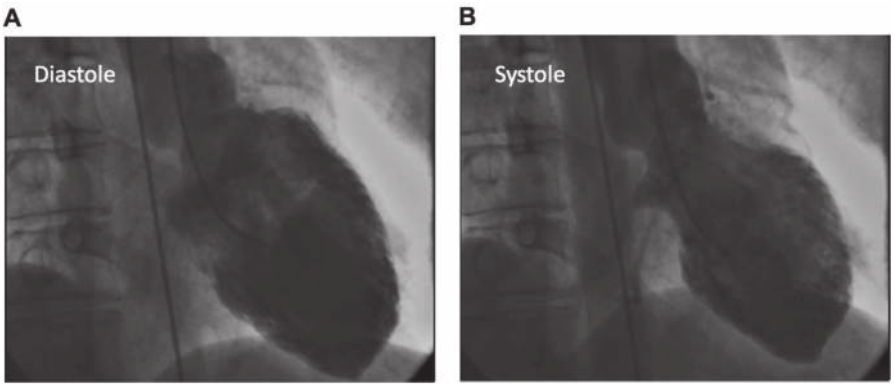

Figure 3. Laevocardiography of TTS patient with typical apical ballooning triggered by emotional stress.

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myocardial perfusion and sympathetic innervation. A reduced mIBG in the dysfunctional myocardial segments during the acute phase is consistent with disturbances in regional sympathetic neuronal activity [53, 54], and its use in diagnosing TTS has been suggested in combination with myocardial perfusion scintigraphy to exclude infarction.

^{18}F-fluorodeoxyglucose (FDG) has been used to study myocardial glucose metabolism by positron emission tomography (PET); however, its current use has been relegated to scientific research [55].

10. Clinical management and therapeutic strategies

The clinical management protocol for Takotsubo syndrome is poorly defined as the debate explaining its pathophysiological evolution is yet to be resolved. As most patients present initially with symptoms of angina pectoris, it has been recommended that the first line of management be directed towards the treatment of possible myocardial ischemia. This essentially entails treatment with anticoagulants such as aspirin and heparin. Once occlusive coronary artery disease has been excluded, the objective of treatment is to minimise complications and ensure optimal supportive care. Patients are usually admitted to the coronary care unit to enable seamless continuous ECG-monitoring, serial lab tests and repeated echocardiographic examinations.

Takotsubo patients constituting a low-risk profile, with insignificant compromise to cardiac function (LVEF > 45%) could be discharged from the hospital early, however, only after a thorough review of the cardiovascular risk factors and heart failure medication. Recent preclinical trials have advocated therapy with beta-blockers such as metoprolol and carvedilol in patients with low-risk [26, 56], unless contraindications to use pre-exist.

Interesting observations in this regard are the results published from a study by Templin et al., where the use of angiotensin-converting enzyme-inhibitors or angiotensin-receptor-blockers, and not beta-blockers, were associated with improved survival [9].

In patients presenting with severely depressed cardiac output and complications associated with the Takotsubo syndrome, it is advised to stop drugs with sympathomimetic properties (e.g. catecholamines and beta-2-agonists). A therapy with beta-blockers has been recommended in hemodynamically stable patients with atrial and ventricular tachyarrhythmias [10], as also in patients with a hemodynamically significant LVOT obstruction (in combination with an alpha-1-recpetor agonist). In severe manifestations like acute cardiogenic shock, options like use of temporary left ventricular assist devices and extracorporeal membrane oxygenation could be considered. The potential of IABP in this scenario has taken a backseat considering the neutral data presented in the recently concluded IABP-SHOCK II Trial.

The use of inotropes, like norepinephrine or dobutamine, is mostly contraindicated in the Takotsubo syndrome; however, experts have recommended treatment with Levosimendan in patients with advancing cardiogenic shock and multi-organ failure [57–61]. The role of

prophylactic anticoagulation with unfractionated or low-molecular weight heparin is also debatable, but experts have suggested that TTS patients with extensive segmental akinesia could be started on a regimen with therapeutic doses of LMWH.

11. Complications

Takotsubo syndrome has been associated with a growing list of complications of varied severity, contributing to its mortality rate. Almost 52% of all patients have been reported to develop some form of complication in course of this disease [62, 63]. These include acute heart failure, left ventricular outflow tract obstruction, cardiogenic shock, arrhythmias, thrombus formation, pericardial effusion, right ventricular involvement and ventricular wall rupture.

Acute heart failure develops in almost 12–45% of all patients with TTS and, in some patients, it is exacerbated by mitral regurgitation and/or left ventricular tract obstruction. Patients could have significantly elevated LVOT gradients (20–140 mmHg), and those with values greater than 40 mmHg are predisposed to develop hypotension and cardiogenic shock. It has been demonstrated that the use of inotropic drugs exacerbates this LVOT obstruction, while beta-blockers decrease it. Around 4–20% of all TTS patients show symptoms of cardiogenic shock, while almost 9% of them document ventricular arrhythmias during the acute phase. Thrombi develop generally 2–5 days after the index event and are known to resolve after 2 weeks of therapeutic anticoagulation (treatment regimen of at least 3 months). There are also instances of patients presenting with a biventricular involvement, which has been associated with a poorer prognosis and a higher frequency of heart failure [10].

12. Prognosis and conclusion

The Takotsubo syndrome is essentially a benign disease and the prognosis is favourable in most patients. The regional wall-motion abnormalities usually resolve spontaneously within a few days to weeks; however, there have been instances where TTS has persisted due to complications associated with apical thrombus formation [64, 65]. Recent studies have demonstrated that the in-hospital death rate ranges between 0 and 8%, while recurrence rates fluctuate anywhere between 0 and 15% [66, 67].

These results have eschewed renewed interest into the study of Takotsubo syndrome and mechanisms contributing to its pathophysiology. Patients are now recommended routine follow-ups after 3–6 months to evaluate the progress of disease and help better understand its evolutionary dynamics.

Limited current knowledge and often contradictory data have fuelled the debate surrounding the Takotsubo syndrome. There is an urgent need for multiple randomised controlled trials and large registries to optimise existing clinical goals and management strategies, and the launch of InterTAK registry is a step forward in this regard.

http://dx.doi.org/10.5772/68037

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