REVIEW

Takotsubo Syndrome: Does the Octopus Trap Hide Dangers?

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Abstract

Takotsubo syndrome (TTS) is a recently identified acute heart syndrome, characterized by regional wall motion abnormalities not justified by the presence of significant coronary artery obstruction. Clinically, TTS closely resembles acute coronary syndromes (ACS) and therefore differential diagnosis may be an important obstacle for its correct clinical management. The prevalence of TTS is estimated to be around 2% of acute myocardial infarctions, and the number of diagnoses has increased in recent years, possibly reflecting our growing understanding of this condition. Given the similarities between TTS and ACS, clinical presentation in these patients is equivocal. However, numerous peculiar traits have been observed, such as the greater prevalence in postmenopausal women and the presence of stressful triggers. Many pathogenetic hypotheses for TTS, such as catecholamine overload and microvascular dysfunction, have been proposed. None of these have been capable of independently explaining the underlying mechanisms. The diagnostic criteria proposed by the Heart Failure Association of the European Society of Cardiology represent a novel attempt to introduce semiquantitative parameters, yet further scientific validation is needed. Contrary to previous opinions, TTS is not always benign, considering the relatively high prevalence of acute complications, an estimated in-hospital mortality similar to that of acute myocardial infarction (1–8%), and a significant rate of recurrences and persistence of symptoms. Clinical management of TTS has been largely based on empirical experience related to ACS, and therefore pharmacological strategies are partially overlapping. An issue of the utmost importance is the lack of randomized prospective data validating diagnostic criteria, risk stratification, and specific therapeutic approaches.

Keywords: Takotsubo syndrome; stress cardiomyopathy; broken-heart syndrome; sex-related myocardial diseases

Introduction

Takotsubo syndrome (TTS) is an acute heart syndrome typically characterized by apical and circumferential mid-ventricular hypokinesia of the left ventricle in the absence of significantly obstructed epicardial coronary arteries [1]. It owes its name to the Japanese *takotsubo*, an octopus trap used by Hiroshima fishermen, whose shape closely resembles that of the left ventricle at the end of systole typical of the disease. In many aspects TTS mimics the clinical presentation and ECG findings of an acute coronary syndrome (ACS) [1], thus some of the legitimacy of the distinction between these two disorders was questioned [2]. Nevertheless, TTS is also termed as a cardiomyopathy, even though patients with TTS do not appear to have a primary muscle disorder or common genetic alteration [1].

The current inability to immediately exclude ACS as a possible diagnosis has an obvious impact on the treatment and clinical management of patients

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with TTS, who may be given drugs with potential adverse effects and without clinical benefit. Beyond these issues, there are many other aspects that need to be studied and clarified. Differently from what was originally believed, TTS is not always benign, and the octopus trap may hide dangers that need to be fully uncovered to effectively protect and treat the patients. Thus, the goal of this review is to analyze the current findings and hypotheses regarding this enigmatic disease, offering preparatory points for the development of future research.

Epidemiology: An Increasingly Recognized Syndrome

Since its first description in 1990 [3], TTS has been observed in several case reports, and more recently many studies have attempted to analyze its frequency in larger cohorts. In 1991 Dote et al. [4] reported five cases of TTS in a study population of 415 consecutive patients with acute myocardial infarction (AMI) who were examined invasively, therefore observing a prevalence of 1.2%. In 2004 a prospective study reported that TTS cases accounted for 2.2% of patients with an initial diagnosis of ST-segment elevation myocardial infarction [5]. Recently, information has emerged whereby the TTS incidence in the United States was assessed with use of data provided by the National Inpatient Sample [6–8]. In particular, Khera et al. [8] analyzed trends in hospitalization, mortality, and characteristics of TTS patients between 2007 and 2012. A three-fold increase in the number of hospitalizations for primary TTS was observed (1642 cases in 2007–5480 in 2012), probably due to a more widespread knowledge of this disease and, consequently, to an increase in diagnoses. Nevertheless, the information gathered from this phenomenon is of the highest clinical value, because it implies that many patients with TTS are still hidden behind an incorrect diagnosis that precludes them from having the right therapies and clinical management.

Clinical Presentation and Triggers: Clues for a Better Understanding of Takotsubo Syndrome

The clinical presentation in TTS closely mimics that of AMI, with symptoms such as chest pain and dyspnea being the most frequent.

Patient Characteristics: A Women's Disease

Numerous studies have shown that most cases of TTS concern postmenopausal women, who usually account for approximately 90% or more of the cases [7–12]. Brinjikji et al. [12] reported that among the 24,701 patients considered in their study, the mean age was 66.9±30.7 years and men tended to be younger than their female counterparts.

From these data it appears that the pathophysiology of TTS may be related to an alteration in the levels of estrogen. This hormone is known to have an important impact on cardiac health, and studies conducted on rats showed that heart rate and blood pressure during stress are controlled by estrogen [13]. As a consequence, it is possible that an estrogen deficiency, typical of the postmenopausal state, may be a predisposing factor in the development of TTS. This theory is supported by the findings of Sato et al. [14], who reported a case of TTS in a woman with Turner's syndrome who had low estrogen levels because of her genetic disease.

Estrogen: The Double Face of an Old Ally?

Seemingly in contrast with what has been reported so far, in 2012 Brenner et al. [15] showed that the estradiol concentration at hospital admission was significantly *higher* in TTS patients than in the control groups, although this increase was transient and disappeared at follow-up. This finding may be at least partially explained by the fact that stressful events can increase the peripheral aromatization of androgens to estrogens. According to Brenner et al., long-term or short-term elevation of estradiol concentration in menopausal women could play the aforementioned protective role toward the vessels, without however managing to prevent the final cardiac insult, and inducing TTS rather than AMI.

Unfortunately, further data supporting this theory are currently unavailable. Moreover, the questions this finding leaves unanswered are many: If high levels of estrogen can participate in causing TTS, why is the percentage of fertile women affected by the disease so small? Could this increase in the

levels of estrogen have been only a transient effect of stress, rather than a trigger of TTS? Future investigations may provide more clarity on this issue.

Symptoms and Stressors: The Importance of Patient History

As previously mentioned, the symptoms of TTS are not specific enough to differentiate it from ACS. Patients with TTS usually present at the hospital with chest pain, dyspnea, and more rarely, syncope [9, 11, 16], all symptoms that are traditionally associated with AMI.

One of the anamnestic elements that could help in orientating the diagnosis toward TTS is the patient's history, especially the evidence of stressful physical conditions or emotional events preceding the symptom onset. These types of stressors tend to be present in the large majority of TTS patients [11, 16], and the incidence of TTS rapidly increases in populations recently hit by earthquakes or other calamities [17, 18]. Physical triggers tend to have a higher frequency than emotional ones (36.0% versus 27.7%) [11], although the line that separates these two types of stressor may not always be so clear. Clinical conditions such as decompensated chronic obstructive pulmonary disease have been reported to induce TTS in several cases [19, 20]: despite being usually considered a physical trigger, this disease also brings fear and anxiety to patients, who during every attack feel they may choke to death. A similar reasoning could be made for other conditions such as stroke, and raises doubts about whether psychological factors should really have been regarded as a less frequent trigger of TTS than physical ones.

The Heart-Breaking Burden of Chronic Stress

Despite not being considered the first trigger of TTS in terms of frequency [11], and even though TTS is not the only cardiovascular disease that may be induced by psychological factors [21], emotional stressors have always been considered an important element in the characterization of the syndrome. However, the seemingly "acute" nature of the events leading to TTS raises an important question:

since most of the modern population has to face acute stressful situations almost daily, why is this syndrome so rare?

It would seem that TTS patients may be "predisposed" toward an exaggerated sensitivity to emotional triggers. Some of the possible mechanisms underlying this phenomenon (such as anxiety, depression, poor stress coping skills and previous exposure to chronic stress) have been investigated, sometimes with discordant results [22–24]. In particular, the "chronic stress" hypothesis was supported by Wallström et al. [23], who in their interviews revealed that TTS patients had experienced constant stress for years or even decades before the onset of symptoms. These chronic stressful situations were unanimously considered by the patients to be more burdensome than the event that had actually triggered the syndrome. Could it then be possible for a prolonged exposure to stressful circumstances to induce vulnerability and susceptibility toward acute psychological or physical stressors? How could this explain the epidemiology of the syndrome, given that chronic stress is also a constant part of our society? Most probably, an explanation will be found in the interaction between psychological/psychosocial factors and physical alterations, as suggested by Kastaun et al. [24], but to prove this theory more elaborate investigations should be undertaken, possibly exploiting the larger registries that have been established in recent years as a source of more consistent cohorts.

Stress and Pathophysiology of TTS

The important role of stressful triggers in the pathophysiology of TTS is suggested by the hyperadrenergic state observed in most patients with the disease. A study in 2005 showed that plasma catecholamine levels at presentation were two-fold to three-fold higher in patients with TTS than in those with Killip III myocardial infarction [25], and TTS has been repeatedly reported in association with diseases or clinical procedures that could induce a hyperadrenergic storm, such as pheochromocytoma, subarachnoid hemorrhage, or alcohol withdrawal [26–29]. An elevated concentration of serum catecholamines, caused by either these conditions or an excessive stress response to surgery or a strong emotion, could lead both to an increase in

myocardial contractility (and/or increased vascular resistances) and to a direct injury of the myocardium caused by calcium overload. According to other theories, elevated levels of epinephrine may have a downregulating effect, possibly via β_2-adrenergic receptor signaling, especially in the apex, where such receptors are more prevalent [30]. This provides a possible explanation for the characteristic distribution of contractile dysfunction.

Is Catecholamine Toxicity Really the Answer?

Despite the pathophysiological theory of catecholamine toxicity in TTS having been widely promoted, there are issues that need to be clarified. Y-Hassan et al. [31] found that only 3 of 33 consecutive TTS patients had markedly elevated catecholamine and/or metabolite levels, and all of them had underlying illnesses or acute complications. These findings contrast with the idea of a causal link between catecholamine toxicity and TTS, but do not exclude the possibility that catecholamines may trigger a cardiac sympathetic hyperactivation: most probably, these serum alterations are, as with estrogen, a single mechanism in the context of a much more complex, multifactorial disease.

Microvascular Dysfunction

Coronary microvascular dysfunction (CMD), an identified pathogenetic factor in ACS, is also among the long list of mechanisms associated with TTS and which may explain its greater incidence in women [32–43]. The diagnostic efficacy of the quantification of coronary flow reserve, by adenosine as a stressor, has been observed in patients with patent coronary arteries, in patients with significant stenosis, and even in those with occluded arteries but effective collateral coronary circulation [44–46]. More recently, quantification of coronary flow reserve to detect either normal coronary flow or impaired coronary circulation due to CMD and dobutamine stress as a means of disclosing myocardial viability (by differentiating it from stunning due to actual ischemia) was proposed as a diagnostic means in TTS [47, 48]. Furthermore, Elesber et al. [49] observed a diffuse CMD that correlated with the extent of myocardial injury during the acute phase of the syndrome, suggesting that CMD, possibly mediated by catecholamine overload, may be an underlying mechanism of myocardial insult and consequent stunning in TTS. Given the high prevalence of neuropsychiatric disorders observed in TTS patients and the direct connection between brain and coronary microcirculation, it remains plausible that this phenomenon represents a key for unlocking the mysteries of this syndrome [11].

An Ageless and Genetic Disorder?

Another interesting phenomenon associated with TTS is its observation in younger age groups such as newborns, children, and adolescents, which does not speak in favor of the hypothesis of atherosclerotic endothelial injury as a causal factor in this syndrome [50–54]. Further observations from case reports of TTS in siblings and relatives are hypothetically indicative of a potential genetic determinant underlying the syndrome, possibly a channelopathy similar to that of Brugada syndrome [55–58]. Although this hypothesis could explain the rarity and possibly the morphology of the disease, further research is still needed for confirmation.

Diagnostic Criteria – the Path Toward a Diagnosis of Certainty

The progression of our understanding of TTS has seen a contemporary evolution of diagnostic criteria, with some characteristics maintaining their importance and others being reinterpreted or becoming obsolete (Table 1).

The Mayo Clinic diagnostic criteria for TTS, introduced in 2004 and revised in 2008, would seem to have become somewhat outdated for various reasons [59, 60]. Firstly, the requirement of extension of regional wall motion abnormality (RWMA) beyond the territory of distribution of a single coronary artery is in contrast with the identification of the focal TTS subtype [61, 62]. Furthermore, the observation that up to 15% of TTS patients have significant coronary artery disease suggests that a more encompassing criterion, such as the *absence of culprit atherosclerotic coronary artery disease*, as stated by the European Society of Cardiology

Table 1 Diagnostic Criteria of Takotsubo Syndrome.

Mayo Clinic

1. Transient hypokinesis, akinesis, or dyskinesis of left ventricular wall segments (mid to apical), which involve a portion larger than a single epicardial arterial distribution. A stressful trigger is common but may not be present.
2. Lack of angiographic evidence of coronary obstructive disease or plaque rupture.
3. Electrocardiographic alterations or slight elevation of cardiac troponin levels.
4. The absence of pheocromocytoma and myocarditis.

Takotsubo Cardiomyopathy Study Group

Definition: Takotsubo (ampulla) cardiomyopathy is a disease exhibiting an acute left ventricular apical ballooning of unknown cause. In this disease, the left ventricle takes on the shape of a "takotsubo" (Japanese octopus trap). There is nearly complete resolution of the apical akinesis in most of the patients within 1 month. The contraction abnormality occurs mainly in the left ventricle, but involvement of the right ventricle is observed in some cases. A dynamic obstruction of the left ventricular outflow tract (pressure gradient difference, acceleration of blood flow, or systolic cardiac murmurs) is also observed.

Note: There are patients, such as cerebrovascular patients, who have an apical systolic ballooning similar to that in Takotsubo cardiomyopathy, but with a known cause. Such patients receive a diagnosis of "cerebrovascular disease with Takotsubo like myocardial dysfunction" and are differentiated from idiopathic cases.

The following lesions and abnormalities from other diseases must be excluded in the diagnosis of Takotsubo (ampulla) cardiomyopathy:

1. Significant organic stenosis or spasm of a coronary artery. In particular, acute myocardial infarction due to a lesion of the anterior descending branch of the left coronary artery, which perfuses an extensive territory including the left ventricular apex. (An urgent coronary angiogram is desirable for imaging during the acute stage, but coronary angiography is also necessary during the chronic stage to confirm the presence or absence of a significant stenotic lesion or a lesion involved in the abnormal pattern of ventricular contraction).
2. Cerebrovascular disease.
3. Pheochromocytoma.
4. Viral or idiopathic myocarditis.

Note: For the exclusion of coronary artery lesions, coronary angiography is required. Takotsubo-like myocardial dysfunction could occur with diseases such as cerebrovascular disease and pheochromocytoma.

References for diagnosis:
1. Symptoms: Chest pain and dyspnea similar to those in acute coronary syndrome. Takotsubo cardiomyopathy can occur without symptoms.
2. Triggers: Emotional or physical stress may trigger Takotsubo cardiomyopathy, but it can also occur without any apparent trigger.
3. Age and sex difference: Known tendency to increase in the elderly, particularly women.
4. Ventricular morphology: Apical ballooning and its rapid improvement in the ventriculogram and echocardiogram.
5. Electrocardiogram: ST-segment elevations might be observed immediately after the onset. Thereafter, in a typical case, the T wave becomes progressively more negative in multiple leads, and the QT interval is prolonged. These changes resolve gradually, but a negative T wave may continue for several months. During the acute stage, abnormal Q waves and changes in the QRS voltage might be observed.
6. Cardiac biomarkers: In a typical case, there are only modest elevations of serum levels of cardiac enzymes and troponin.
7. Myocardial radionuclear study: Abnormal findings in myocardial scintigraphy are observed in some cases.
8. Prognosis: Most patients recover rapidly, but in some cases pulmonary edema and other sequelae or death occurs.

Johns Hopkins University School of Medicine

Mandatory criteria (all three criteria must be met):

1. Absence of coronary thrombosis or angiographic evidence of acute plaque rupture
2. Regional ventricular wall motion abnormalities that extend beyond a single epicardial vascular distribution
3. Complete recovery of regional wall motion abnormalities (recovery is usually within days to weeks)

Helpful, but not mandatory, criteria:

1. An acute identifiable trigger (either emotional or physical)
2. Characteristic ECG changes that may include some or all of the following:
   a. ST-segment elevation at the time of admission (often 2 mm in magnitude, and usually not associated with reciprocal ST-segment depression)

<div align="center">**Table 1** (continued)</div>

    b. Diffuse deep T-wave inversion (may be present on admission or may evolve during the first several hospital days)
    c. QT interval prolongation (usually maximal by 24–48 h)
3. Mildly elevated cardiac troponin levels (often appears disproportionately low given the degree of wall motion abnormality)

University of Gothenburg

1. Transient hypokinesis, akinesis, or dyskinesis in the left ventricular segments and frequently, but not always, a stressful trigger (psychical or physical)
2. The absence of other pathological conditions (e.g., ischemia, myocarditis, toxic damage, tachycardia, etc.) that more credibly explain the regional dysfunction
3. No elevation or modest elevation of cardiac troponin level (i.e., disparity between the troponin level and the amount of dysfunctional myocardium)
4. Normal or near normal left ventricular filling pressure*
5. Low or near normal peripheral vascular resistance and normal or near normal cardiac output*

Takotsubo Italian Network

1. Typical transient left venticular wall motion abnormalities extending beyond a single epicardial vascular distribution with complete functional normalization within 6 weeks
2. Absence of potentially culprit coronary stenosis, or angiographic evidence of acute plaque rupture, dissection, thrombosis, or spasm**
3. New and dynamic ST-segment abnormalities or T-wave inversion as well as new onset of transient or permanent left bundle branch block
4. Mild increase in the levels of myocardial injury markers (creatine kinase MB value <50 U/L)
5. Clinical and/or instrumental exclusion of myocarditis
6. Postmenopausal woman (optional)*
7. Antecedent stressful event (optional)*

European Society of Cardiology Heart Failure Association

1. Transient regional wall motion abnormalities of left venticular or right venricular myocardium which are frequently, but not always, preceded by a stressful trigger (emotional or physical).
2. The regional wall motion abnormalities usually† extend beyond a single epicardial vascular distribution, and often result in circumferential dysfunction of the ventricular segments involved.
3. 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 left ventricular dysfunction observed (e.g., hypertrophic cardiomyopathy, viral myocarditis).
4. New and/or reversible ECG abnormalities (ST-segment elevation, ST-segment depression, left bundle branch block,‡ T-wave inversion, and/or corrected QT prolongation) during the acute phase (3 months).
5. Significantly elevated serum natriuretic peptide levels (BNP or NT-proBNP) during the acute phase.
6. Positively but relatively small elevation in cardiac troponin level measured with a conventional assay (i.e., disparity between the troponin level and the amount of dysfunctional myocardium present).§
7. Recovery of ventricular systolic function on cardiac imaging at follow-up (3–6 months).‖

From [1, 59–64].
BNP, B-type natriuretic peptide; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide.
*Optional diagnostic criteria that are not mandatory, but when positive they increase the likelihood of Takotsubo syndrome diagnosis.
**Coronary angiography should be performed as soon as possible (ideally within 48 h of admission).
†Acute, reversible dysfunction of a single coronary territory has been reported.
‡Left bundle branch block may be permanent after Takotsubo syndrome, but should also alert clinicians to exclude other cardiomyopathies. T-wave changes and corrected QT prolongation may take many weeks to months to normalize after recovery of left ventricular function.
§Troponin-negative cases have been reported, but are atypical.
‖Small apical infarcts have been reported. Bystander subendocardial infarcts have been reported, involving a small portion of the acutely dysfunctional myocardium. These infarcts are insufficient to explain the acute regional wall motion abnormality observed.

(ESC) Heart Failure Association position statement, may be more effective [1, 11, 63]. Lastly, differentiating TTS from pheochromocytoma-induced cardiomyopathy is too restrictive, for many cases of TTS in these patients have been observed [25–27].

The 2007 Japanese Takotsubo Cardiomyopathy Group criteria defined TTS as idiopathic, distinguishing it from TTS-like cases associated with known causes [64]. In our opinion the conceptual separation between TTS and TTS-like cases does not respect the syndromic nature of the disease, considering the clinical differences are minimal. Lastly, these criteria were formulated with the assistance of a questionnaire that could possibly predispose to a criteria selection bias.

In 2012, Wittstein [65] of the Johns Hopkins University School of Medicine published criteria somewhat similar to those proposed by the Mayo Clinic, with slight differences such as the separation of helpful and mandatory factors. The inclusion of cardiac imaging evidence of restored ventricular systolic function within a predetermined time frame may be helpful in certain cases; however, signs of short-term recovery, such as ECG characteristics, serum marker levels, or radionuclide imaging findings, may be more clinically useful during the acute phase, when complications have been found to be most frequent. The Gothenburg criteria, introduced in 2011 and recently revised, have brought some interesting measurable factors into consideration, such as left ventricular filling pressure and peripheral vascular resistance and cardiac output [66]. This novel attempt to introduce quantitative units of measurement is an important insight and represents the desirable direction of progression in terms of identifying more specific clinical criteria.

In 2014, the Takotsubo Italian Network proposal for diagnostic criteria was published, containing a series of intriguing novelties, alongside a number of shortcomings inherited from previous criteria [67]. Worthy of note is the attempt to quantify biomarker level elevation and the recovery period, even though, as stated before, the latter is less useful in the acute phase. Subsequent to great demand, in 2015, the ESC Heart Failure Association adapted and revised previous models to formulate the TTS diagnostic criteria, which comprise several previously defined factors but have also included a series of footnotes capable of making these criteria more

encompassing [1]. For example, the ubiquitous and characteristic circumferential RWMA is required, but the existence of focal abnormalities was also recognized. On the other hand, semiquantitative criteria, such as significant elevation of serum natriuretic peptide levels and moderate increase in cardiac troponin levels, represent an important step toward the use of measurable markers for TTS diagnosis. The standard diagnostic approach to TTS is transitioning away from a diagnosis of exclusion with the identification of more TTS-"specific" characteristics, such as the circumferential nature of ventricular dysfunction and other clinical patterns. Despite these advancements, measurable diagnostic parameters and evidence of their validity are still lacking; therefore prospective comparative analyses are needed to formulate novel and verify proposed clinical scores [68].

Diagnostic Procedures

The ESC Heart Failure Association has also proposed a novel diagnostic algorithm, for the identification and differentiation of TTS patients that may help clinicians navigate through this difficult diagnosis [1]. Most TTS patients have typical ECG abnormalities, such as ST-segment elevation, T-wave inversions, and pathological Q waves [9, 69]. Hypoglycemia, a known cause of TTS, is also associated with catecholamine surge and corrected QT interval prolongation, both of which are frequently present in patients with TTS [53, 70–72]. Some authors have proposed a series of ECG characteristics as having a high sensitivity and specificity for TTS; however, prospective data are needed to verify their predictive capacity [68, 69].

Coronary Angiography and Left Ventriculography – Identification of Typical Morphology

Considering the profound clinical similarities between TTS and AMI, coronary angiography remains the standard invasive procedure for the exclusion of culprit coronary artery stenosis in the acute setting [63]. In addition, the identification of wall motion abnormalities by left ventriculography may be of help for diagnosis. However, it should be noted that, given the limits of ventriculography in delineating the true

extent of RWMAs in both the left ventricle and the right ventricle, diagnoses should be coadjuvated by echocardiography and possibly cardiac magnetic resonance imaging, given the higher diagnostic power of these two noninvasive procedures.

Echocardiography

Transthoracic echocardiography has been shown to contribute to a more frequent diagnosis of TTS given its capacity to identify left ventricular morphology and function, anatomical variants, and coronary flow reserve, as well as to detect correlated complications in the acute phase, such as left ventricular outflow tract obstruction, right ventricular involvement, apical thrombosis, mitral regurgitation, and cardiac rupture [30, 47, 48, 73]. Furthermore, typical RWMAs, which correlate with the extent of myocardial insult and suggest a circumferential morphology, and wall motion score index, which has been observed to positively correlate with the extent of ST-segment elevation, have been found to differentiate AMI from TTS with a significant specificity and sensitivity [73–75].

Two-dimensional speckle tracking echocardiography has played an important role in the study of ventricular morphology and in the identification of the circumferential nature of RWMAs [75].

An interesting diagnostic alternative might be the use of stress testing with low doses of dobutamine in combination with enoximone, which has been found to be at least as efficient as full-dose dobutamine, yet safer, in ACS patients [76].

Adjunctive Imaging

Cardiac magnetic resonance imaging can be of assistance in the initial diagnosis of TTS, given its capacity to accurately assess left and right ventricular RWMAs, distinguish irreversible and reversible myocardial damage, and identify the distinct transmural, midventricular to apical pattern [77–79]. These characteristics can be of assistance in differentiating TTS from AMI and myocarditis, and therefore cardiac magnetic resonance imaging should be used in synergy with coronary angiography and echocardiography.

Nuclear imaging techniques have been found not only to have a valid application in differential diagnosis between TTS and AMI but have had a substantial role in studying the pathogenetic mechanisms associated with TTS as well. Various studies have shown a typical pattern in TTS patients, referred to as "inverse flow metabolism mismatch," characterized by a severely reduced apical myocardial uptake of glucose and by a moderately reduced myocardial perfusion [80, 81]. Additionally, TTS patients were found to have a severe denervation, measured with [123]I- metaiodobenzylguanidine single photon emission computed tomography [81]. Ito el al. [82] compared TTS and AMI metabolic characteristics and concluded that the transitory nature of TTS suggests similarities with myocardial stunning. However, given the high rate of false positives of single photon emission computed tomography perfusion imaging in the detection of myocardial infarction with concurrent wall motion abnormalities and reduced ventricular wall thickness, which are frequently dominant characteristics in TTS, nuclear imaging should be preceded or the nuclear imaging findings should be confirmed by cardiac magnetic resonance imaging in these patients [83, 84].

Laboratory Testing – Searching for Measurable Markers

The level of serum cardiac biomarkers may assist the clinician in differentiating TTS and AMI. Said biomarkers can be present in both TTS and AMI but, given the extent of ventricular dysfunction, the elevation of their levels is considered disproportionately low in TTS [11, 59].

As previously stated, an elevation in catecholamine serum levels is thought to be one of the main driving forces in TTS [25–27]; therefore dosing catecholamine levels may facilitate the identification of dubious cases. B-type natriuretic peptide serum levels, which have the advantage of correlating with myocyte distension rather than necrosis [85], have been shown to increase in TTS to a greater extent than in AMI [86]. However, when a similar extent of wall motion abnormality is present, B-type natriuretic peptide values in AMI can resemble those seen in TTS.

Specific microRNA patterns have been widely observed in both cardiovascular and noncardiovascular diseases [87]. A comparison between the

elevation and/or depression of the levels of cardiac-specific microRNAs has shown TTS-specific patterns that may potentially be useful in differential diagnosis with AMI [88]. This novel diagnostic approach will, nonetheless, require further prospective data for its validation.

Prognosis: Not as Harmless as It Seemed

Left ventricular dysfunction in TTS is typically a transient phenomenon, so TTS has historically been considered harmless. However, most of the studies currently at hand show that the octopus trap is more dangerous than previously thought [89, 90]. Firstly, the rate of acute complications such as heart failure, arrhythmias, mitral regurgitation, cardiogenic shock, and cardiac rupture is rather high, although data on their incidence differ widely [8, 11, 12]. Brinjikji et al. [12] reported that the prevalence of acute complications was 34.5%, and that the most frequent complication was acute coronary heart failure (31.1%), more frequent in women than in men and occasionally accompanied by respiratory insufficiency (6.7%). Others have observed independent predictors of low and high incidence of acute complications [11]. The ESC Heart Failure Association position statement introduced a promising risk stratification tool aimed at the prediction of complications in TTS patients, although additional prospective and comparative studies are needed for its validation [1].

Mortality among TTS patients is yet another element that should warn clinicians about the potential harmfulness of the syndrome. In-hospital mortality differs widely from study to study, ranging from 1% to 8%, which are rates actually similar to those of AMI patients [12, 91–97]. According to Brinjikji et al. [12], mortality tended to rise in patients with acute complications and in those with underlying critical illnesses. Moreover, although no correlation was found between death and age or ethnicity, it was observed that men had higher mortality and were likelier to have underlying critical illnesses and acute complications (except for coronary heart failure).

Elesber et al. [97] found that chest pain recurred in 31% of TTS patients at follow-up, and that the average annual recurrence rate of TTS was 2.9% in the first 4 years and 1.3% at the end of the follow-up. Singh et al. [91] reported similar recurrence rates (1.5%), although the percentage of patients with recurrent chest pain was lower (14%).

Therapy: From Empirical to Evidence Based

Initial therapy is usually directed toward AMI, and patients often begin treatment with aspirin, anticoagulants, beta-blockers, and possibly angiotensin-converting enzyme (ACE) inhibitors. If the presence of plaque rupture is compatible with TTS, then long-term antiplatelet therapy may be reasonably justified. Similarly, in consideration of the absence of beneficial effects and excessive bleeding risks, thrombolytic therapies should be avoided in patients with TTS [63]. Therapy with beta-blockers and ACE inhibitors or angiotensin receptor blockers may be continued or introduced in the aim of preventing or treating acute complications such as arrhythmias, severe heart failure, or left ventricular outflow tract obstruction [1, 63]. However, Templin et al. [11] observed beneficial effects on long-term survival associated with ACE inhibitor or angiotensin receptor blocker administration, but did not find the same association with beta-blocker therapy. This suggests that prospective randomized data are needed not only to verify the ideal management of the acute phase but also to identify efficient long-term prevention in TTS patients. Furthermore, the relatively high incidence of complications in TTS justifies thorough evaluation of risk and attentive monitoring to enable timely and efficient prevention and treatment. The European Heart Failure Takotsubo Task Force has recently elaborated diagnostic and therapeutic algorithms, based on expert consensus, the latter of which considers different strategies for low-risk and high-risk patients [1].

Use of sympathomimetic agents and inotropes should be avoided or discontinued, because of the possible exacerbation of cardiac damage given that at higher concentrations an excessive inhibitory G-protein stimulation is obtained [98–101]. Severe cases of heart failure and shock may be treated with mechanical support devices or with levosimendan [102] when these are not available; given

the efficacy of intra-aortic balloon counterpulsation in AMI is controversial [1, 63, 103–105], its efficiency in TTS patients should be studied prospectively along with that of other mechanical support devices.

Patients with significant apical akinesis or apical RWMA should be considered for prophylactic antithrombotic therapy, which will most likely have been initiated at admission and should be continued until RWMAs have resolved [1, 63].

Limited data on prophylactic therapy for recurrences and persistent symptoms exist, and therefore randomized prospective data are needed to verify the ideal therapeutic strategies for both short-term and long-term management.

Conclusions

Many theories have been proposed to explain the pathogenetic model underlying TTS but, while some of these hypotheses seem to be more plausible than others, the complete mechanism underlying the syndrome is not fully understood. It would seem that catecholamine overdrive may be an important component in the manifestation of TTS, but this theory does not explain the relative rarity of the syndrome. Could it be that some sort of preexisting condition is necessary to "predispose" people to the development of TTS? Could it be logical to hypothesize the presence of genetic determinants, such as a congenital channelopathy or adrenergic receptor polymorphisms? Or could TTS be favored by an environmental predisposing condition, such as chronic stress, manifested as an alteration in microRNA expression?

Considering that these and many other questions regarding TTS are yet to be answered, and taking into account the presence of various conditions associated with TTS, such as CMD, neuropsychiatric disorders, and other comorbidities, evidence suggests that the pathogenic mechanisms in TTS are multifactorial and representative of the delicate balance between various intimately tied components of the human organism. It is likely that future breakthroughs in the understanding of such mechanisms will come not only from the field of cardiology but that a significant contribution will emerge from interdisciplinary studies and observations.

Despite the growing attention that TTS has attracted in recent years and the increasing number of promising research studies regarding its clinical management, prospective randomized studies have been scarce, largely related to the rarity of this syndrome, and there is lack of universally acknowledged data on aspects such as diagnostic criteria, risk stratification, and therapeutic regimens. Future resources should be invested in the production and validation of effective, evidence-based guidelines that will help clinicians in the battle against this mysterious and insidious disease and its sometimes difficult differentiation from ACS.

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Conflict of Interest

The authors declare no conflict of interest [106–108].

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