Cardiovascular Revascularization Medicine 20 (2019) 70–79

Contents lists available at ScienceDirect

Cardiovascular Revascularization Medicine

Review

Takotsubo syndrome: State-of-the-art review by an expert panel – Part 1

Andre Dias [a,b], Ivan J. Núñez Gil [c], Francesco Santoro [d], John E. Madias [e], Francesco Pelliccia [f], Natale Daniele Brunetti [d], Elena Salmoirago-Blotcher [g], Scott W. Sharkey [h], Ingo Eitel [i], Yoshihiro J. Akashi [j], Ibrahim El-Battrawy [k,l], Emiliana Franco [b], Ibrahim Akin [k,l], Milosz Jaguszewski [m], Dana Dawson [n], Vincent M. Figueredo [b], L. Christian Napp [o], Thomas Emil Christensen [p], Kathy Hebert [q], Itsik Ben-Dor [a], Yuichi Ozaki [a], Héctor M. García-Garcia [a], Alexandre H. Kajita [a], Takashi Akasaka [r], Satoshi Kurisu [s], Amir Lerman [t], Ron Waksman [a,*]

[a] *Section of Interventional Cardiology, MedStar Washington Hospital Center, Washington, DC, United States of America*
[b] *Department of Cardiology, Einstein Medical Center, Philadelphia, PA, United States of America*
[c] *Interventional Cardiology, Cardiovascular Institute, Hospital Clínico San Carlos, Madrid, Spain*
[d] *Department of Medical & Surgery Sciences, University of Foggia, Foggia, Italy*
[e] *Icahn School of Medicine at Mount Sinai/Division of Cardiology, Elmhurst Hospital Center, Elmhurst, NY, United States of America*
[f] *Interventional Cardiology Unit, Sapienza University, Rome, Italy*
[g] *Centers for Behavioral and Preventive Medicine, The Miriam Hospital, Warren Alpert Medical School of Brown University, Providence, RI, United States of America*
[h] *Minneapolis Heart Institute Foundation, Minneapolis, MN, United States of America*
[i] *Cardiology, Angiology, Intensive Care Medicine, University Lübeck, Schleswig-Holstein, Germany*
[j] *Division of Cardiology, Department of Internal Medicine, St. Marianna University School of Medicine, Kawasaki, Kanagawa, Japan*
[k] *Department of Internal Medicine, University Heidelberg, Mannheim, Germany*
[l] *DZHK (German Center for Cardiovascular Research), Partner Site, Heidelberg-Mannheim, Germany*
[m] *Department of Cardiology, Medical University of Gdansk, Poland*
[n] *School of Medicine and Dentistry, University of Aberdeen, Aberdeen, UK*
[o] *Department of Cardiology and Angiology, Hannover Medical School, Hannover, Germany*
[p] *Copenhagen University Hospital, Copenhagen, Denmark*
[q] *GE Healthcare, Miami, FL, United States of America*
[r] *Department of Cardiovascular Medicine, Wakayama Medical University, Wakayama, Japan*
[s] *Department of Cardiovascular Medicine, Hiroshima University, Hiroshima, Japan*
[t] *Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN, United States of America*

ARTICLE INFO

Article history:
Received 14 November 2018
Accepted 14 November 2018

Keywords:
Takotsubo
Heart failure
Catecholamine

ABSTRACT

Takotsubo syndrome (TTS) is an acute cardiac condition independent of epicardial coronary obstruction that mimics acute coronary syndrome and is characterized by acute heart failure with reversible ventricular motion abnormalities. This consensus paper is the result of a multinational effort aiming to summarize the current state of the art on TTS. Experts in the field provide a thorough and detailed review of this syndrome. Several novel and unique sections are emphasized in this document, including the current state of the art on genetics of takotsubo syndrome, microRNAs (miRs), racial differences, role of cardiac spectroscopy and intracoronary imaging, as well as mechanical circulatory support.

In part 1 of this two-part manuscript, we discuss how TTS came to be known, several patterns and forms it can take in patients, epidemiology and pathophysiology of the syndrome, and clinical presentation.

Contents

1. Introduction . . . 71
1.1. Historical perspective . . . 71

Abbreviations: ACS, acute coronary syndrome; BNP, B-type natriuretic peptide; CRP, C-reactive protein; LV, left ventricle/ventricular; MACE, major adverse cardiac events; miRs, microRNAs; RV, right ventricle/ventricular; STEMI, ST-elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction; TTS, Takotsubo syndrome.

* Corresponding author at: MedStar Heart and Vascular Institute, MedStar Washington Hospital Center, 110 Irving St., NW, Suite 4B-1, Washington, DC 20010, United States of America.
E-mail address: ron.waksman@medstar.net (R. Waksman).

https://doi.org/10.1016/j.carrev.2018.11.015
1553-8389/

1.2. Nomenclature . . . 71
1.3. Diagnostic criteria . . . 72
2. The different patterns of takotsubo . . . 73
2.1. Anatomical variants . . . 73
2.2. Primary and secondary forms . . . 73
3. Epidemiology . . . 74
3.1. Prevalence . . . 74
3.2. Inpatient morbidity . . . 74
3.3. Inpatient mortality . . . 74
3.4. Gender differences . . . 74
3.5. Age disparity . . . 74
3.6. Racial disparities . . . 74
3.7. Malignancy association . . . 75
3.8. Genetic perspective . . . 75
4. Pathophysiology . . . 75
4.1. Catecholamine surge . . . 75
4.2. Beta receptors mechanism and myocardial ischemia . . . 75
4.3. Depressed cardiac energetic measured with 31 P cardiac spectroscopy . . . 75
4.4. Role of hormonal/reproductive factors . . . 76
4.5. Inflammation and interleukins' role in TTS . . . 76
4.6. Low prevalence of diabetes in TTS patients . . . 77
5. Clinical presentation . . . 77
5.1. Primary and secondary forms . . . 77
5.2. Right ventricle involvement . . . 77
5.3. Inverted forms . . . 77
5.4. Potential triggers . . . 77
5.5. Pharmacologic triggers . . . 77
5.6. Procedure-related triggers . . . 77
Declarations of interest . . . 77
Funding . . . 78
References . . . 78

1. Introduction

1.1. Historical perspective

Takotsubo syndrome (TTS) was described for the first time decades ago [1]. In 1986, a female case of transient left ventricular apical wall motion abnormalities after her son's suicide was reported from United States [2]. In this case, coronary angiography revealed no significant stenosis. Similar conditions complicated by pheochromocytoma or subarachnoid hemorrhage were already recognized around that time [3,4].

In 1990, Dr. Hikaru Sato first recognized the mysterious condition of reversible left ventricular apical wall motion abnormalities without coronary artery disease, which was often associated with emotional or physical stress, and proposed the term “takotsubo-like left ventricular dysfunction” from Hiroshima City Hospital. This name derives from the shape of systolic left ventriculogram resembling a takotsubo (Fig. 1) [5].

After 2000, Japanese researchers introduced knowledge of this disorder outside Japan with English papers [6,7], and the concept and name “takotsubo cardiomyopathy” became recognized worldwide.

1.2. Nomenclature

TTS is a peculiar condition that clinically mimics an acute coronary syndrome (chest pain, heart failure, ECG changes, biomarkers) with reversible ventricular motion abnormalities [8].

The main feature is the absence of coronary artery findings potentially responsible and, usually, the involvement of myocardium territories dependent on various coronary arteries. Most researchers describe it as a myocardial stunning process, possibly secondary to catecholamine injury [8–10].

Initially TTS was deemed to be a cardiomyopathy, but some scientists criticized the fact that the term implies a primary disease of the myocardium and proposed to define it as an acute and usually reversible heart failure syndrome [10].

However, although the condition does not seem to be a “primary disease” of the cardiac muscle – in most cases, at least – or we have not yet identified a clear genetic basis, the fact that most of the patients do not present heart failure symptoms makes it difficult to accept the latter definition [9–11]. Others, consider that the problem is a transient cardiomyopathy, since a number of recurrences have been reported and some underlying pathophysiologic abnormalities at the myocardium level have been described, explaining why only some people develop the syndrome after intense stressful situations [12].

Moreover, due to its clinical heterogeneity (clinical profile, different triggers, different anatomic forms, left ventricle or right ventricle or RV

Fig. 1. A takotsubo used for trapping octopuses in Japan (Courtesy Dr. Kurisu S).

variable involvement, different pathophysiology) it could be a cluster of different diseases with similar expression (phenocopies), fulfilling the definition of “syndrome” [9,11–13].

The entity has commonly received several names, with >30 reported [13,14], highlighting among them: takotsubo cardiomyopathy or syndrome, Ampulla syndrome or transient cardiac/apical ballooning because of the LV shape (Japanese octopus pot) in the imaging techniques, transient apical dyskinesia, and broken heart syndrome or stress cardiomyopathy due to its clear link with stressful situations.

The term “stress cardiomyopathy” has the problem that, frequently, we are not able to find a particular stress as trigger and that there are other catecholaminergic situations, such as pheochromocytoma, that are frequently excluded as takotsubo syndromes [13–16].

We support the unifying term suggested for this disease as “takotsubo syndrome,” despite not all patients having the typical “takotsubo trap” shape in their ventricles [10].

1.3. Diagnostic criteria

Since the syndrome description in 1986, several sets of diagnostic criteria have been published, usually making the syndrome an “exclusion diagnosis” [17] that entered into National Center for Biotechnology Information (NCBI) databases as a distinct clinical entity in 2008 [17]. Among these criteria stand out the Mayo criteria (2004, modified and simplified in 2008) [18], the Japanese Takotsubo Cardiomyopathy Group (2007) [6], the Johns Hopkins criteria (2012) [19], the Gothenburg Group (2013) [20], the Takotsubo Italian Network (2014) [21], those proposed by Madias [22] and, most recently, the Heart Failure Association of the European Society of Cardiology Takotsubo Syndrome Diagnostic Criteria in 2015 [10], which added the elevation of serum natriuretic peptide as a separate criterion.

Currently, the most widely used criteria are the 2008 modified Mayo criteria (i.e., InterTAK [23], Retako [24]). However, in this set, the presence of pheochromocytoma is considered an exclusion criterion while, in fact, several authors consider those cases to be within the takotsubo spectrum [16,18]. Probably, a simplified set of diagnostic criteria for a syndromic approach followed by a diagnostic workup in order to get a more precise etiological diagnosis would be warranted, as we do with dilated myocardiopathy, for example [12]. Interestingly, more recently, a genetic basis has been suggested to be involved in TTS with several familial cases of and small studies reporting a potential association between TTS and several genes [25–29].

Our proposed working algorithm including a simplified set of criteria, is displayed in Fig. 2.

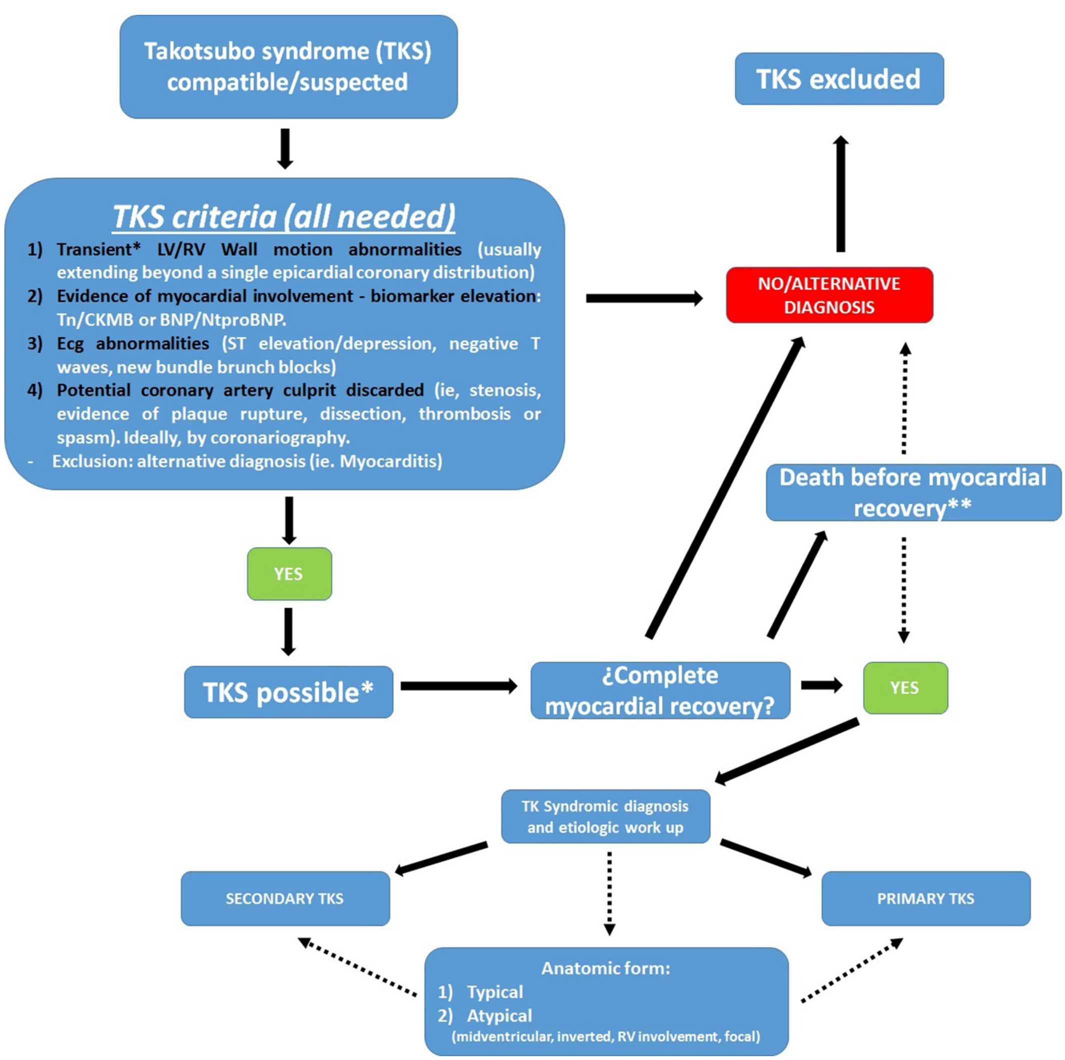

Fig. 2. Working algorithm proposed including a simplified set of diagnostic criteria. *Transient refers to a variable period of time ranging from days to weeks until a complete myocardial recovery is depicted by imaging techniques. **If a patient dies before an established diagnosis, the complete clinical profile (comorbidities, stressful situation) must be assessed.

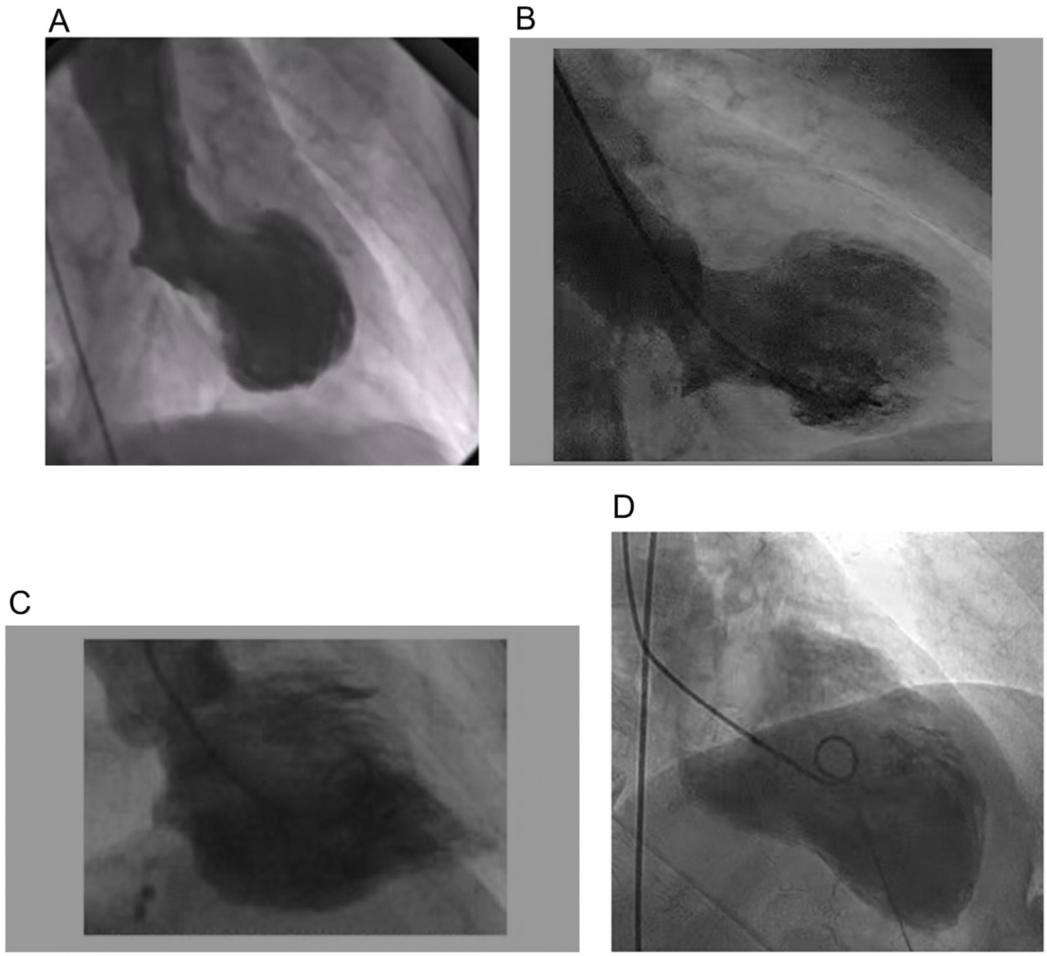

Fig. 3. A – *Apical (classic) pattern* – End-systolic image from left ventriculography. B – *Mid ventricular* – End-systolic image from left ventriculography. C – *Inverted or basal type* – End-systolic image from left ventriculography. D – *Focal type* – end-systolic image from left ventriculography.

2. The different patterns of takotsubo

2.1. Anatomical variants

Since this initial description of apical ballooning, also known as the classical pattern, and characterized by apical akinesis or hypokinesis with preserved and/or hypercontractile basal segments, several different types of left ventricular involvement have been described [23,30,31].

1) **Classical pattern** – Present in up to 80% of patients. (Fig. 3A).
2) **Mid-ventricular pattern** – Characterized by hypokinesis of the mid left ventricle and hypercontractile apical and basal segments. Present in up to 15% of patients. (Fig. 3B).
3) **Inverted (reverse) or basal pattern** – Characterized by basal and mid-ventricular segment hypokinesis or akinesis with preserved contractility or hypercontractility of apical segments. Present in 2–5% of patients (Fig. 3C).
4) **Focal type** – Characterized by hypokinesis or akinesis of an isolated segment; usually an anterolateral segment. Present in up to 1.5% of patients (Fig. 3D).
5) **Atypical patterns including right ventricular involvement** – Includes apical tip sparing variant, biventricular apical dysfunction, isolated RV involvement and global type. Their prevalence is unknown, but likely represents a small minority of TTS cases [23,32,33].

Probably, the most useful classification on this regard comprises 2 main types:

The most common or **typical form** – takotsubo pot-shaped, with apical affectation – and the first type described. Usually occurs in 70–85% cases, being 81.7% in the largest series published, over 1750 patients (InterTAK) [23,24]. The imaging techniques depict a distinctive LV apical and mid-ventricular dis/a/hypokinesia together with basal hypercontractility.

The **atypical forms**, less frequent and heterogeneous, usually sparing the apex cordis [34]. We could include in this type those with mid-ventricular affectation – about 15% – and, less frequently, the basal type (also known as inverted or reverse, “nutmeg” or “artichoke” heart) often related to neurologic comorbidities – e.g., subarachnoid hemorrhage – or pheochromocytoma [32]; global and focal types; and, finally, those with right ventricular affectation (biventricular or rarely isolated right involvement). Also, there was described a case of “double takotsubo,” where the typical form was followed by the inverted type [33].

The clinical RV expression is rare [10]. Some authors have reported that RV contractile abnormalities may follow the same LV regional distribution and could influence the prognosis [10]. It is possible that the RV affectation, observed about in 25–30% of the cases in some series, evolved unnoticed in some cases. In fact, a recent small study with 31 patients reported that visually, echocardiography was able to identify only 52% of patients who showed RV wall motion abnormalities on cardiac magnetic resonance [35].

2.2. Primary and secondary forms

The anatomic classification can be complemented by another simple distinction between primary and secondary forms [10,12]. This is intended to be a more etiologic grouping and thus would probably have management and prognostic value. Although the concept varies slightly among clinicians and researchers, we can assume these two separate groups of takotsubo syndromes [10,12]:

Primary forms – In this group of patients, the most common (about 80% in a 2016 Retako analysis of 328 patients) [12], the acute cardiac symptoms are the primary reason for seeking medical attention. These patients do not have clearly identifiable triggers (28.5% over 1750 cases in InterTAK [36]) or when present, the stressful triggers are emotional/psychic (27.7% in InterTAK) [36].

Secondary forms – Those with physical factors or comorbidities, potentially acting as directly responsible for the cardiac condition (asthma, drugs, surgery, trauma, subarachnoid hemorrhage, hyperthyroidism, pheochromocytoma or paraganglioma, etc.) [10,36–38]. Some consider these cases as takotsubo phenocopies.

3. Epidemiology

3.1. Prevalence

TTS may occur in up to 2% of patients presenting with suspected acute coronary syndrome (ACS) [9,23]. The fact that it commonly presents with signs and symptoms resembling an ACS poses an important diagnosis challenge since the distinction between these two entities is frequently not immediately evident.

Despite initially being considered a relatively benign condition, more current data have shown that TTS may be associated with considerable inpatient morbidity and carry a small but important mortality risk [23]. The prevalence of TTS has been increasing worldwide, especially among Caucasians. This is likely a consequence of an improved awareness of the existence of this syndrome and easier access to early coronary angiography than a true increase in TTS incidence [9,10,23]. Prior studies have consistently shown that TTS affects predominantly postmenopausal women (66–80 years). The most common clinical symptoms are chest pain (67%) and dyspnea (17%). TTS patients also have higher frequencies of psychiatric disorders, such as depression and/or anxiety, in comparison to ACS patients [23,39].

3.2. Inpatient morbidity

According to data from the Nationwide Inpatient Sample (NIS-USA) (2008–2009 and 2009–2010), considered one of largest reported cohorts, a higher mortality was observed in men, likely related to an increased prevalence of acute critical illnesses, ventricular arrhythmia, and sudden cardiac arrest [18,39]. Of note, TTS patients were identified based on the International Classification of Diseases (ICD) discharge codes and not on a systematic and detailed review of each individual clinical case, which could potentially lead to inconsistencies in TTS diagnosis. As per the International Takotsubo Registry (group of 26 centers in Europe and the United States) which included a total of 1750 TTS patients, cardiogenic shock may affect 4.2% and ventricular fibrillation 1.5% of cases [9,23].

Acute respiratory failure, acute neurologic or psychiatric diseases, physical triggers, higher troponin levels, and lower ejection fraction on admission were independent predictors for in-hospital complications [23,39,40].

3.3. Inpatient mortality

In the literature, the reported in-hospital mortality ranges from 1 to 5%, depending on the series. However, according to more recent data from larger registries, TTS may carry 30-day mortality in the range of 4–6%, which is considered comparable to ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI) [23].

3.4. Gender differences

TTS is more frequent in women than men, predominantly affecting postmenopausal females. According to the International Takotsubo Registry, TTS exhibits a female-to-male ratio of approximately 9:1. Overall, male and female TTS patients have similar demographics and clinical characteristics; however, they do have some important differences worth mentioning. Physical triggers are more prevalent in men, whereas emotional triggers are more common in women. Acute neurological disorders, such as intracranial bleeding, are more frequently seen in men [23,41,42].

In-hospital complications, such sepsis, ventricular arrhythmias, the need for invasive or noninvasive ventilation, and the use of catecholamines, are more common among men. Cardiac arrest on presentation, particularly out-of-hospital cardiac arrest, is also reported more frequently in men.

In-hospital mortality and rate of major adverse cardiac events (MACE) have been consistently higher in men than in women [23]. During the first 30 days after admission, men remain at higher risk of MACE and all-cause mortality than women [9,23,40].

Long-term follow-up has also shown that men have an increased rate of all-cause mortality and major adverse cardiac and cerebrovascular events beyond 30 days.

3.5. Age disparity

Women have significantly higher odds of developing TTS, and the vast majority (up to 80%) are older than 50 years of age. In a study of 6837 patients diagnosed with TTS among 33,506,402 hospitalizations in the Nationwide Inpatient Sample database – using discharge records in 2008 using the International Classification of Diseases, Ninth Revision, code 429.83 – older women (>55 years) had 10.7 times higher odds of developing TTS in comparison to men of similar age and 4.8 times higher odds for developing TTS when compared with women <55 years old [18,23,43,44]. In men, there was no significant association of age with development of TTS. At the time of TTS diagnosis, men are usually younger than women [23].

Potential changes in the density and responsiveness of local myocardial adrenergic receptors from base to apex during menopause could account for some of the gender and age differences noted [23]. Overall, elderly patients have a higher prevalence of comorbid cardiovascular conditions and worse in-hospital major adverse cardiovascular outcomes such as acute heart failure, life-threatening arrhythmias, stroke, lower ejection fraction upon admission, and cardiogenic shock [23,40].

3.6. Racial disparities

There is a relative paucity of data regarding the potential impact of race and/or ethnicity in TTS presentation and outcomes. However, after European and North American TTS registries started publishing their data, it became evident that race and ethnicity could play an important role in TTS [44].

Caucasians present more commonly with chest pain and after an emotional trigger in comparison to other racial groups. Asians and African-Americans may have a higher rate of in-patient complications, such as stroke and acute respiratory failure, requiring mechanical ventilation in comparison to Caucasians and Hispanics [23,44].

Distinctive racial electrocardiographic differences have also been reported in these registries, with T-wave inversion and QT prolongation being more prevalent among African-Americans. Higher prevalence of ST-segment elevation has been observed in Asians, whereas ST-segment depression is more frequently seen in non-African-Americans. Prospective clinical trials are needed to confirm these findings [23,44,45].

3.7. Malignancy association

Noteworthy, evidence now exists that patients with TTS have an elevated rate of malignancy that greatly exceeds the expected prevalence of cancer in age-matched populations in the United States and European countries [46–48].

In their pivotal work, Burgdorf et al. reported that patients with TTS more commonly had a previous diagnosis of malignancy or developed malignancies during follow-up as compared with patients with acute myocardial infarction [49]. Similarly, El-Sayed et al. found that patients with TTS have higher odds of malignancy than orthopedic and myocardial infarction patients in a large population of patients hospitalized with TTS in the United States over a 2-year period [50]. The results of the COUNT study, an international collaborative review including a large series of 1109 patients with TTS, found that the frequency of malignancy ranged from 4 to 29% (average: 10%) [51].

More recently, it has been shown that those TTS patients with a diagnosis of malignancy have higher peak BNP, leukocyte levels, CRP and experience a higher mortality rate [52]. These findings provide a reliable confirmation of the hypothesis that malignancy predisposes to TTS [53]. Although the exact mechanisms of action of malignancy remain speculative, a number of clinical and experimental studies have convincingly elucidated the potential links between cancer and emotional stress, inflammation, and neurohormonal activation in TTS [54]. Indeed, cancer is accompanied by increased psychological stress, which in turn increases susceptibility to TTS.

3.8. Genetic perspective

Several familial cases of TTS have been described [25]. The recently identified genetic variants in key cardiac regulator genes imply a genetic predisposition in TTS through increased sensitivity to catecholamine toxicity. Moreover, other reasons that make a genetic predisposition in TTS reasonable are a) There have been several reports of familial cases [25,26]; b) TTS recurs in 5–10% of patients, suggesting a genetically mediated vulnerability; c) Most postmenopausal women experience acute stressful events, but only a small subset develop TTS.

Small studies in individual patients have reported an association between TTS and several genes, including Bcl-2–associated athanogene 3 (BAG3) [26]. However, conflicting results have been published in small studies regarding the presence or absence of functional polymorphisms in relevant candidate genes, such as α1-, β1-, and β2-adrenergic receptors, G-protein coupled receptor kinase (GRK)-5, and estrogen receptors [27].

The first genome-wide association study (GWAS) in TTS patients identified potential genetic risk variants and found promising preliminary results, but the study was too small to draw definite conclusions [28]. Another recent study investigated a genetic predisposition for TTS by using an in vitro induced pluripotent stem cell (iPSC) model of TTS [29]. Several genetic variants in different key regulators of cardiac function could be uncovered, including an overactive β-adrenergic pathway and higher sensitivity of catecholamines in TS iPSC-CMs and TTS engineered heart muscle [29]. Receptor desensitization and different β_1/β_2-AR were identified as potentially important pathophysiological components of TTS. According to current available data, it is likely that a genetic predisposition may interact with environmental factors, polygenic etiology and/or recessive susceptibility alleles; however, small genetic studies have failed to identify significant causative genetic variants [27,55]. A small number of case reports suggest an association between rare genetic syndromes and TTS [55–57].

4. Pathophysiology

4.1. Catecholamine surge

Catecholamine surge constitutes one of the most intriguing features of TTS [31]. Both circulating epinephrine and norepinephrine released from the adrenal medulla and norepinephrine released locally from sympathetic nerves are increased in the acute phase of TTS. This catecholamine surge leads, through multiple mechanisms, to myocardial damage, which is the substrate of transient apical left ventricular ballooning (Fig. 4).

Acute emotional and/or physical stressors, i.e., the well-known triggers of TTS, have been shown to induce brain activation, thus increasing epinephrine and norepinephrine levels [46]. Specifically, the stress-induced increase in norepinephrine secretion stimulates the hypothalamic-pituitary-adrenal axis, causing adrenal medullary cells to synthesize and release predominantly epinephrine. Plasma levels of catecholamines and their metabolites are elevated in the acute phase of TTS in nearly 75% of patients, as originally demonstrated by Akashi et al. [58], and subsequently reported by Wittstein et al. [59].

Along with higher levels of circulating catecholamine, there is also evidence of increased catecholamine at the myocardial level in the acute phase of TTS. Kume et al. have demonstrated increased norepinephrine spillover in the coronary sinus in a small series of patients with TTS, suggesting increased local myocardial release of catecholamine from cardiac nerve endings [60]. Indeed, norepinephrine spillover from the cardiac sympathetic nerves induces calcium overload, thus resulting in contraction band necrosis – one of the pathological hallmarks of TTS [61].

4.2. Beta receptors mechanism and myocardial ischemia

Catecholamine surge acts on beta-adrenergic receptors, which in turn affect chronotropic, inotropic, and lusitropic cardiac functions and trigger the onset of LV dysfunction [46]. Regional differences in density of different types of adrenergic receptors seem to explain the typical pattern of left ventricular dysfunction often seen in TTS. The beta2-adrenergic receptors are more frequently expressed in apical than in basal segments of the left ventricle, whereas a reverse distribution is present for norepinephrine beta1-adrenergic receptors, which are expressed mainly at the base than at the apex of the left ventricle [10].

Both epinephrine and norepinephrine have positive inotropic effects through Gs-coupling protein. The rise in levels of epinephrine trigger beta2-adrenoceptors to switch from Gs to Gi coupling, which is associated with a negative inotropic response of the left ventricular apex [10]. This mechanism protects left ventricular myocardium from the catecholamine storm, thus limiting the degree of myocardial injury in the acute phase of TTS [10].

A further pathogenetic mechanism of TTS is transient myocardial ischemia. Since the 1990s, epicardial coronary artery spasm and/or diffuse coronary vasoconstriction have commonly been reported in most series of patients from Japan. Indeed, development of coronary spasm with acetylcholine testing has been found in patients with TTS [37]. Also, spontaneous coronary artery dissection is reported with increasing frequency in patients with TTS [62].

Recently, microvascular dysfunction has been advocated as a further pathogenetic determinant of myocardial ischemia in TTS based on the evidence that invasive and noninvasive diagnostic tools have documented abnormal coronary microvascular responses in TTS [48]. The demonstration of reduced TIMI (Thrombolysis in Myocardial Infarction) frame count at emergency coronary angiography, the finding of perfusion defect in the left ventricular segments showing reduced contractility with myocardial contrast echocardiography, the evidence of a decrease in tracer uptake during the acute phase of TTS, and a return to normal at follow-up with single-photon emission computed tomography strongly suggest a role for coronary microvascular dysfunction as a trigger of myocardial ischemia in this condition [31].

4.3. Depressed cardiac energetic measured with 31 P cardiac spectroscopy

There is little mechanistic evidence regarding the acute intramyocyte pathophysiology processes that occur and evolve in the

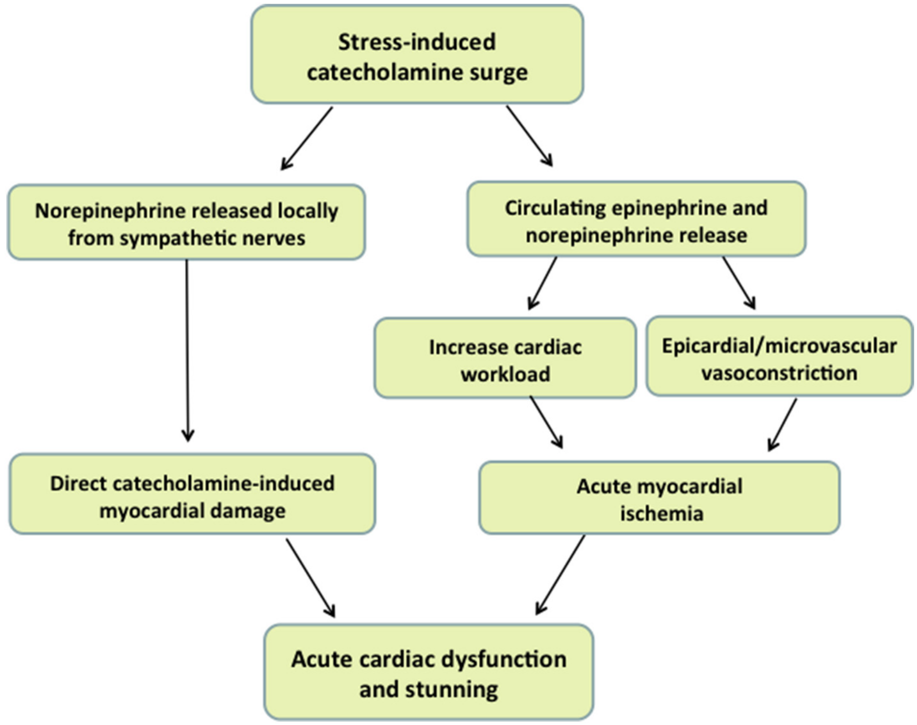

Fig. 4. Pathophysiology of TTS: Acute emotional and/or physical stressors cause an acute catecholamine surge, with an increase in myocardial release of catecholamine as well as a raise in circulating epinephrine and norepinephrine levels. Endogenous catecholamine released into the heart via nerve terminals cause a direct catecholamine-induced myocardial toxicity. The catecholamine surge acts on beta-adrenergic receptors thus affecting chronotropic, inotropic, and lusitropic cardiac functions. Also, catecholamine surge with excessive cardiac sympathetic activity can induce either epicardial coronary artery spasm or diffuse coronary microvascular constriction, thus contributing to the acute myocardial dysfunction and stunning.

human takotsubo heart beyond that of small myocardial biopsies [63], which have been collected predominantly from the right ventricle due to the high risk posed by performing a biopsy from an akinetic or dyskinetic myocardial territory.

Nevertheless, it has been demonstrated that myocardial energetics (the phosphocreatine/gamma-adenosine triphosphate (PCr/γATP) ratio obtained non-invasively by ^{31}P-cardiac magnetic resonance spectroscopy) is severely reduced in acute TTS patients [64].

This occurs alongside a strikingly edematous myocardium [64,65].

While it is well-known that a fundamental characteristic of the human takotsubo heart is a prompt and spontaneous recovery of the left ventricular ejection fraction, the recovery of the cardiac energetics as well as that of the myocardial edema appears to lag behind that of the ejection fraction, since residual levels of edema have been shown to persist at 4 months in the regions that were acutely affected and, in addition, there is only partial recovery of the cardiac energetic status at 4 months post-index event [64].

4.4. Role of hormonal/reproductive factors

Animal studies showing that estrogen supplementation reduces the incidence of TTS in response to emotional stress [66,67] have led researchers to hypothesize that reproductive factors could play a role in the onset of TTS.

To date, however, there is very limited information in humans, and the few clinical studies examining the role of hormonal/reproductive factors in the development of TTS have several limitations (i.e., small sample size, retrospective design).

A small study compared estradiol, progesterone, luteinizing hormone, and follicle-stimulating hormone levels in women with TTS, MI, and healthy women and found – unexpectedly – higher concentrations of estradiol in TTS compared to both controls [68]. Estrogen levels, though, were measured at admission and likely increased in response to stress [68].

A retrospective case-control study found no differences in the prevalence of menopausal status, frequency of oophorectomy, and average years since the onset of menopause across female TTS cases, age- and event date-matched female controls with ST-segment elevation myocardial infarction, and women with neither diagnosis [69].

Another small prospective case-control study compared reproductive characteristics of TTS female cases, MI controls, and healthy women [70]. TTS women more frequently reported a history of irregular menses and menopausal symptoms, higher parity, and using hormone replacement therapy compared to MI and healthy female controls.

In multivariable adjusted models, a history of irregular menses, parity, and use of postmenopausal hormone replacement were significantly associated with the onset of TTS.

The absence of associations between TTS and a history of oophorectomy, and the fact that the use of hormone replacement therapy was not protective, suggest that in contrast with animal studies [66,67], estrogen levels per se may not play a role in the physiopathology of TTS in humans. Instead, this study suggested a possible important association between premenopausal factors (e.g., disruptions in ovulatory cycling, parity) and the onset of TTS at a later age.

4.5. Inflammation and interleukins' role in TTS

An inflammatory reaction is observed during the acute phase of TTS, but its role is still not clearly defined. Catecholamines may cause endothelial damage with consequent release of growth factors (VEFG and EFG) and interleukins [71].

Higher serum levels of interleukins 6 and 10 at TTS admission are associated with risk of in-hospital complications and adverse events at follow-up [72]. When compared with acute myocardial infarction (AMI), TTS is featured by higher prevalence of macrophages (CD68) and anti-inflammatory interleukins during both the acute and recovery phases [63].

4.6. Low prevalence of diabetes in TTS patients

It has been postulated that patients with diabetes mellitus (DM) with complicated ASNS peripheral neuropathy would either be protected from suffering TTS or experience mild forms of the disease. Accordingly, patients with TTS would be expected to have a low prevalence of DM; also, patients with DM who have suffered TTS would be expected to have mild and/or short-duration DM, and certainly without complicating ASNS neuropathy.

To explore this, a meta-analysis of 33,894 patients (88.9% women) with TTS reported between 2001 and February 22, 2014, was carried out, employing 5 subanalyses (all patients, patients reported individually, patients reported collectively in case series, patients <60 years old reported individually, and patients >65 years old reported individually. The prevalence of DM was 16.8%, 10.2%, 17.0%, 11.9%, and 12.5%, correspondingly, and lower than the 26.9% found by the National Health and Nutrition Examination Survey (NHANES) [47].

5. Clinical presentation

5.1. Primary and secondary forms

When we divide TTS patients between primary and secondary forms, we are probably separating different diseases (phenocopies) and thus will obtain different clinical presentations and prognoses. Recent data have shown that "primary" patients suffered more frequent chest pain as the main complaint (89.4% vs. 50.7%, $p < 0.0001$) with vegetative symptoms (57.4% vs. 38.1%; $p = 0.006$). Palpitations, syncope or heart failure/shock on admission were numerically more frequent in secondary forms.

During admission, differences were related to more intensive antithrombotic and anxiolytic drug use in the primary group. Inotropic and mechanical ventilation use was higher in the secondary forms, which also displayed higher biomarker elevation and more in-hospital stay and evolutive complications (death, recurrences) [12].

5.2. Right ventricle involvement

Up to 34% of TTS patients may have some degree of RV involvement, even if not immediately clinically apparent [10]. Biventricular involvement is typically identified on imaging studies such as echocardiography and MRI. In observational retrospective studies, the most frequently affected RV segments were the apico-lateral, antero-lateral and inferior walls [23]. The presence of RV involvement has been associated with a higher prevalence of in-hospital major adverse cardiovascular events, including heart failure, cardiogenic shock, and in-hospital mortality [23,34]. RV involvement is more prevalent in older patients with a lower baseline left ventricular ejection fraction and is associated with higher frequency of significant or bilateral pleural effusions [23,34].

5.3. Inverted forms

Inverted (Reverse) or Basal Pattern: Patients with an inverted or basal pattern are younger and more commonly present with an identifiable emotional or physical triggering event in comparison to TTS patients presenting with the classical pattern [37]. Heart failure symptoms and significant mitral regurgitation are less prevalent in the inverted forms [37] while subarachnoid hemorrhage may be more common [38]. More recent data suggest that some atypical forms, particularly the reverse patterns, may carry worse prognosis [10].

5.4. Potential triggers

Both emotional and physical events are established triggers, although more recently, an increasing association with physical stressors has emerged, as well as the realization that the condition may occur spontaneously, without an identifiable trigger, in a minority of patients. Triggering events, particularly those of a personal nature, may be concealed at the time of presentation [73,74].

In the Minneapolis Heart Institute experience of nearly 400 TTS patients, 10% provided no history of a triggering event, physical stressors were present in 50%, and emotional events in 40% [73]. In comparison, a report from the International Takotsubo Registry [23] noted triggering events as physical in 36%, emotional in 28%, both in 8%, and neither in 29%. The rising importance of physical triggers of TTS likely reflects greater awareness of this condition occurring in a health-care environment in association with an acute illness, medication administration, medical testing, or an invasive procedure.

The diversity of precipitating events associated with TTS ranges from the ordinary to the catastrophic; furthermore, seemingly minor events can act as a trigger [23,73,75].

5.5. Pharmacologic triggers

Drugs with a variety of pharmacologic actions, ranging from chemotherapeutic agents to antidepressants, have been reported as TTS triggers, often when administered in accidental or deliberate overdose [10,23,42]. Illicit drug use (cocaine) and withdrawal from drugs (alcohol, opioids, metoprolol) are also known triggers [36,73].

Catecholamine administration in both therapeutic and excessive doses has been temporally related to TTS onset.

Among the endogenous catecholamines, epinephrine has received the most attention, likely reflecting the widespread use of this drug in health-care settings. In most cases, epinephrine was administered during a minor surgical procedure, although reports of intentional overdose during suicide attempt exist [10,76].

Norepinephrine overdose has also been reported to induce TTS [77]. The synthetic catecholamines dobutamine, isoproterenol, and salbutamol have each been reported to provoke TTS, most commonly when used during stress testing, electrophysiologic testing, or treatment of chronic obstructive lung disease and asthma [10,76].

Notably, intraocular injection of phenylephrine has been reported as a takotsubo trigger [10,76]. These takotsubo-catecholamine administration events provide support for the potential participation of the sympathetic nervous system in the mechanism of TTS.

5.6. Procedure-related triggers

The evidence for TTS complicating medical or surgical procedures is extensive and ranges from minor (colonoscopy) to major (prolonged spinal surgery) [23,40]. Ironically, procedures performed by cardiologists and cardiothoracic surgeons are regularly reported TTS triggers, including dobutamine stress testing, pericardiocentesis, cardioversion of atrial fibrillation, pacemaker insertion, electrophysiologic testing and ablation, and surgical and transcatheter valve replacement [10,16].

It is important, therefore, to consider TTS when encountering patients with hemodynamic or rhythm instability after cardiovascular procedures. Resuscitation from cardiac arrest represents a particularly profound physiologic stress, frequently requiring epinephrine administration and defibrillation, each of which can itself trigger a TTS event [16].

Declarations of interest

Milosz Jaguszewski, MD, FESC, has received lecture honoraria from St. Jude Medical.

Dana Dawson, DM, FRCP, DPhil, FESC, has a research agreement with Philips Healthcare and holds an MTA with AMAG Pharmaceuticals.

L. Christian Napp, MD, received lecture honoraria from Abiomed, Maquet and Cytosorbents, consultant fees from Bayer, and traveling or

congress support from Abbott, Abiomed, Bayer, Biotronik, Boston Scientific, Lilly, Medtronic, Merit Medical, Pfizer, Servier, and Volcano.

Kathy Hebert, MD, MPH, is an employee of GE Healthcare.

Takashi Akasaka, MD, has received lecture fees and research funds from Kowa Pharmaceutical Co. Ltd.

Ron Waksman, MD, received honoraria from Abbott Vascular, Amgen, Boston Scientific, Chiesi, Medtronic and Philips Volcano, and consulting fees from Biosensors, Biotronik, Corindus, Lifetech Medical and Pi-Cardia LTD. He is on the advisory boards of Abbott Vascular, Amgen, Boston Scientific, Medtronic, Philips Volcano and Pi-Cardia LTD, is a consultant for Abbott Vascular, Amgen, Biosensors, Biotronik, Boston Scientific, Corindus, Lifetech Medical, Medtronic, Philips Volcano and Pi-Cardia LTD, received grant support from Abbott Vascular, Biosensors, Biotronik, Boston Scientific, Chiesi and Edwards Lifesciences, and is an investor in MedAlliance.

All other authors have no conflicts of interest to disclose.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

[1] Tokioka M, Miura H, Masaoka Y, Nishizaki S, Mikouchi H, Nishizaki Y, et al. Transient appearance of asynergy on the echocardiogram and electrocardiographic changes simulating acute myocardial infarction following non-cardiac surgery. J Cardiogr 1985 Sep;15(3):639–53.
[2] Ryan TJ, Fallon JT. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 18–1986. A 44-year-old woman with substernal pain and pulmonary edema after severe emotional stress. N Engl J Med 1986 May 8;314(19):1240–7.
[3] Takada K, Seino Y, Shimai S, Tanaka K, Kato T, Takano T, et al. A case report of pheochromocytoma showing AMI like ECG changes and transient apical defect on 201-T1 myocardial SPECT. Nippon Naika Gakkai Zasshi 1987 Aug;76(8):1256–63.
[4] Pollick C, Cujec B, Parker S, Tator C. Left ventricular wall motion abnormalities in subarachnoid hemorrhage: an echocardiographic study. J Am Coll Cardiol 1988 Sep;12(3):600–5.
[5] Dote K, Sato H, Tateishi H, Uchida T, Ishihara M. Myocardial stunning due to simultaneous multivessel coronary spasms: a review of 5 cases. J Cardiol 1991;21(2):203–14.
[6] Kawai S, Kitabatake A, Tomoike H, Takotsubo Cardiomyopathy Group. Guidelines for diagnosis of takotsubo (ampulla) cardiomyopathy. Circ J 2007 Jun;71(6):990–2.
[7] Ito K, Sugihara H, Kawasaki T, Yuba T, Doue T, Tanabe T, et al. Assessment of ampulla (Takotsubo) cardiomyopathy with coronary angiography, two-dimensional echocardiography and 99mTc-tetrofosmin myocardial single photon emission computed tomography. Ann Nucl Med 2001 Aug;15(4):351–5.
[8] Sharkey SW, Lesser JR, Zenovich AG, Maron MS, Lindberg J, Longe TF, et al. Acute and reversible cardiomyopathy provoked by stress in women from the United States. Circulation 2005 Feb 1;111(4):472–9.
[9] Nunez Gil IJ, Andres M, Almendro Delia M, Sionis A, Martin A, Bastante T, et al. Characterization of Tako-tsubo cardiomyopathy in Spain: results from the RETAKO National Registry. Rev Esp Cardiol (Engl Ed) 2015 Jun;68(6):505–12.
[10] Lyon AR, Bossone E, Schneider B, Sechtem U, Citro R, Underwood SR, et al. Current state of knowledge on Takotsubo syndrome: a Position Statement from the Taskforce on Takotsubo Syndrome of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2016 Jan;18(1):8–27.
[11] Nunez-Gil IJ, Molina M, Bernardo E, Ibanez B, Ruiz-Mateos B, Garcia-Rubira JC, et al. Tako-tsubo syndrome and heart failure: long-term follow-up. Rev Esp Cardiol (Engl Ed) 2012 Nov;65(11):996–1002.
[12] Nunez-Gil IJ, Almendro-Delia M, Andres M, Sionis A, Martin A, Bastante T, et al. Secondary forms of Takotsubo cardiomyopathy: a whole different prognosis. Eur Heart J Acute Cardiovasc Care 2016 Aug;5(4):308–16.
[13] Mejia-Renteria HD, Nunez-Gil IJ. Takotsubo syndrome: advances in the understanding and management of an enigmatic stress cardiomyopathy. World J Cardiol 2016 Jul 26;8(7):413–24.
[14] Sharkey SW, Lesser JR, Maron MS, Maron BJ. Why not just call it tako-tsubo cardiomyopathy: a discussion of nomenclature. J Am Coll Cardiol 2011 Mar 29;57(13):1496–7.
[15] Movahed MR. Transient cardiac ballooning is not best nomenclature for Takotsubo cardiomyopathy as it does not capture all variants of this syndrome. Stress cardiomyopathy is a much better term for this syndrome. Clin Cardiol 2010 Apr;33(4):241–2 [author reply 242].
[16] Sharkey SW, McAllister N, Dassenko D, Lin D, Han K, Maron BJ. Evidence that high catecholamine levels produced by pheochromocytoma may be responsible for Tako-Tsubo cardiomyopathy. Am J Cardiol 2015 Jun 1;115(11):1615–8.
[17] Scantlebury DC, Prasad A. Diagnosis of Takotsubo cardiomyopathy. Circ J 2014;78(9):2129–39.
[18] Prasad A, Lerman A, Rihal CS. Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction. Am Heart J 2008 Mar;155(3):408–17.
[19] Wittstein IS. Stress cardiomyopathy: a syndrome of catecholamine-mediated myocardial stunning? Cell Mol Neurobiol 2012 Jul;32(5):847–57.
[20] Redfors B, Shao Y, Omerovic E. Stress-induced cardiomyopathy (Takotsubo)–broken heart and mind? Vasc Health Risk Manag 2013;9:149–54.
[21] Parodi G, Citro R, Bellandi B, Provenza G, Marrani M, Bossone E, et al. Revised clinical diagnostic criteria for Tako-tsubo syndrome: the Tako-tsubo Italian Network proposal. Int J Cardiol 2014 Mar 1;172(1):282–3.
[22] Madias JE. Why the current diagnostic criteria of Takotsubo syndrome are outmoded: a proposal for new criteria. Int J Cardiol 2014 Jul 1;174(3):468–70.
[23] Templin C, Ghadri JR, Diekmann J, Napp LC, Bataiosu DR, Jaguszewski M, et al. Clinical features and outcomes of Takotsubo (stress) cardiomyopathy. N Engl J Med 2015 Sep 3;373(10):929–38.
[24] Nunez Gil IJ, Andres M, Almendro Delia M, Sionis A, Martin A, Bastante T, et al. Characterization of Tako-tsubo cardiomyopathy in Spain: results from the RETAKO National Registry. Rev Esp Cardiol (Engl Ed) 2015 Jun;68(6):505–12.
[25] Kumar G, Holmes Jr DR, Prasad A. "Familial" apical ballooning syndrome (Takotsubo cardiomyopathy). Int J Cardiol 2010 Oct 29;144(3):444–5.
[26] Citro R, D'Avenia M, De Marco M, Giudice R, Mirra M, Ravera A, et al. Polymorphisms of the antiapoptotic protein bag3 may play a role in the pathogenesis of tako-tsubo cardiomyopathy. Int J Cardiol 2013 Sep 30;168(2):1663–5.
[27] Spinelli L, Trimarco V, Di Marino S, Marino M, Iaccarino G, Trimarco B. L41Q polymorphism of the G protein coupled receptor kinase 5 is associated with left ventricular apical ballooning syndrome. Eur J Heart Fail 2010 Jan;12(1):13–6.
[28] Eitel I, Moeller C, Munz M, Stiermaier T, Meitinger T, Thiele H, et al. Genome-wide association study in takotsubo syndrome - preliminary results and future directions. Int J Cardiol 2017 Jun 1;236:335–9.
[29] Borchert T, Hubscher D, Guessoum CI, Lam TD, Ghadri JR, Schellinger IN, et al. Catecholamine-dependent beta-adrenergic signaling in a pluripotent stem cell model of Takotsubo cardiomyopathy. J Am Coll Cardiol 2017 Aug 22;70(8):975–91.
[30] Dawson DK. Acute stress-induced (takotsubo) cardiomyopathy. Heart 2017 Aug;20.
[31] Pelliccia F, Kaski JC, Crea F, Camici PG. Pathophysiology of Takotsubo syndrome. Circulation 2017 Jun 13;135(24):2426–41.
[32] Gervais MK, Gagnon A, Henri M, Bendavid Y. Pheochromocytoma presenting as inverted Takotsubo cardiomyopathy: a case report and review of the literature. J Cardiovasc Med (Hagerstown) 2015 Jan;16(Suppl. 2):S113–7.
[33] Ehl NF, Zurek M, Rickli H, Maeder MT. "Double takotsubo": first description of the sequence of classical followed by inverted type in a young woman. Int J Cardiol 2014 Jun 15;174(2):e36–7.
[34] Ghadri JR, Cammann VL, Napp LC, Jurisic S, Diekmann J, Bataiosu DR, et al. Differences in the clinical profile and outcomes of typical and atypical Takotsubo syndrome: data from the International Takotsubo Registry. JAMA Cardiol 2016 Jun 1;1(3):335–40.
[35] Scally C, Ahearn T, Rudd A, Neil CJ, Srivanasan J, Jagpal B, et al. Right ventricular involvement and recovery after acute stress-induced (Tako-tsubo) cardiomyopathy. Am J Cardiol 2016 Mar 1;117(5):775–80.
[36] Coddens J, Van Alphen J, Deloof T, Hendrickx J. Dynamic left ventricular outflow tract obstruction caused by afterload reduction induced by intra-aortic balloon counterpulsation. J Cardiothorac Vasc Anesth 2002;16:749–51.
[37] Angelini P. Reverse, or inverted, transient Takotsubo cardiomyopathy: terms and status of an open discussion. Tex Heart Inst J 2013;40(1):60–3.
[38] Elgendy AY, Elgendy IY, Mansoor H, Mahmoud AN. Clinical presentations and outcomes of Takotsubo syndrome in the setting of subarachnoid hemorrhage: a systematic review and meta-analysis. Eur Heart J Acute Cardiovasc Care 2016 Nov;16.
[39] Sharkey SW, Maron BJ. Epidemiology and clinical profile of Takotsubo cardiomyopathy. Circ J 2014;78(9):2119–28.
[40] Sharkey SW, Windenburg DC, Lesser JR, Maron MS, Hauser RG, Lesser JN, et al. Natural history and expansive clinical profile of stress (tako-tsubo) cardiomyopathy. J Am Coll Cardiol 2010 Jan 26;55(4):333–41.
[41] Dias A, Franco E, Figueredo VM, Hebert K. Can previous oophorectomy worsen the clinical course of takotsubo cardiomyopathy females? Age and gender-related outcome analysis. Int J Cardiol 2014 Dec 20;177(3):1134–6.
[42] Dias A, Franco E, Figueredo VM, Hebert K, Quevedo HC. Occurrence of Takotsubo cardiomyopathy and use of antidepressants. Int J Cardiol 2014 Jun 15;174(2):433–6.
[43] Schneider B, Athanasiadis A, Stollberger C, Pistner W, Schwab J, Gottwald U, et al. Gender differences in the manifestation of tako-tsubo cardiomyopathy. Int J Cardiol 2013 Jul 1;166(3):584–8.
[44] Dias A, Franco E, Koshkelashvili N, Pressman GS, Hebert K, Figueredo VM. Racial and ethnic differences in Takotsubo cardiomyopathy presentation and outcomes. Int J Cardiol 2015 Sep 1;194:100–3.
[45] Franco E, Dias A, Koshkelashvili N, Pressman GS, Hebert K, Figueredo VM. Distinctive electrocardiographic features in African Americans diagnosed with Takotsubo cardiomyopathy. Ann Noninvasive Electrocardiol 2016 Sep;21(5):486–92.
[46] Wittstein IS, Thiemann DR, Lima JA, Baughman KL, Schulman SP, Gerstenblith G, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. N Engl J Med 2005 Feb 10;352(6):539–48.
[47] Madias JE. Low prevalence of diabetes mellitus in patients with Takotsubo syndrome: a plausible 'protective' effect with pathophysiologic connotations. Eur Heart J Acute Cardiovasc Care 2016 Apr;5(2):164–70.
[48] Pelliccia F, Greco C, Vitale C, Rosano G, Gaudio C, Kaski JC. Takotsubo syndrome (stress cardiomyopathy): an intriguing clinical condition in search of its identity. Am J Med 2014 Aug;127(8):699–704.
[49] Burgdorf C, von Hof K, Schunkert H, Kurowski V. Regional alterations in myocardial sympathetic innervation in patients with transient left-ventricular apical ballooning (Tako-Tsubo cardiomyopathy). J Nucl Cardiol 2008 Jan–Feb;15(1):65–72.

[50] El-Sayed AM, Brinjikji W, Salka S. Demographic and co-morbid predictors of stress (takotsubo) cardiomyopathy. Am J Cardiol 2012 Nov 1;110(9):1368–72.

[51] Pelliccia F, Parodi G, Greco C, Antoniucci D, Brenner R, Bossone E, et al. Comorbidities frequency in Takotsubo syndrome: an international collaborative systematic review including 1109 patients. Am J Med 2015 Jun;128(6):654.e11–9.

[52] Sattler K, El-Battrawy I, Lang S, Zhou X, Schramm K, Tulumen E, et al. Prevalence of cancer in Takotsubo cardiomyopathy: short and long-term outcome. Int J Cardiol 2017 Jul 1;238:159–65.

[53] Madias JE. What is/are the trigger(s) of takotsubo syndrome in cancer patients receiving chemotherapy? Int J Cardiol 2016 Nov 1;222:253.

[54] Burgdorf C, Nef HM, Haghi D, Kurowski V, Radke PW. Tako-tsubo (stress-induced) cardiomyopathy and cancer. Ann Intern Med 2010 Jun 15;152(12):830–1.

[55] Limongelli G, D'Alessandro R, Masarone D, Maddaloni V, Vriz O, Minisini R, et al. Takotsubo cardiomyopathy: do the genetics matter? Heart Fail Clin 2013 Apr;9(2):207–16 [ix].

[56] Eitel I, Friedrich MG. T2-weighted cardiovascular magnetic resonance in acute cardiac disease. J Cardiovasc Magn Reson 2011 Feb 18;13 (13-429X-13-13).

[57] Kushiro T, Saito F, Kusama J, Takahashi H, Imazeki T, Tani S, et al. Takotsubo-shaped cardiomyopathy with type I CD36 deficiency. Heart Vessels 2005 May;20(3):123–5.

[58] Akashi YJ, Nef HM, Lyon AR. Epidemiology and pathophysiology of Takotsubo syndrome. Nat Rev Cardiol 2015 Jul;12(7):387–97.

[59] Wittstein IS, Thiemann DR, Lima JA, Baughman KL, Schulman SP, Gerstenblith G, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. N Engl J Med 2005 Feb 10;352(6):539–48.

[60] Kume T, Akasaka T, Kawamoto T, Yoshitani H, Watanabe N, Neishi Y, et al. Assessment of coronary microcirculation in patients with takotsubo-like left ventricular dysfunction. Circ J 2005 Aug;69(8):934–9.

[61] Basso C, Thiene G. The pathophysiology of myocardial reperfusion: a pathologist's perspective. Heart 2006 Nov;92(11):1559–62.

[62] Madias JE. Spontaneous coronary dissection misdiagnosed as, or triggering, or triggered by, Takotsubo syndrome? Catheter Cardiovasc Interv 2017 May 2;92:E206–7.

[63] Nef HM, Mollmann H, Kostin S, Troidl C, Voss S, Weber M, et al. Tako-Tsubo cardiomyopathy: intraindividual structural analysis in the acute phase and after functional recovery. Eur Heart J 2007 Oct;28(20):2456–64.

[64] Dawson DK, Neil CJ, Henning A, Cameron D, Jagpal B, Bruce M, et al. Tako-Tsubo cardiomyopathy: a heart stressed out of energy? JACC Cardiovasc Imaging 2015 Aug;8(8):985–7.

[65] Eitel I, Lucke C, Grothoff M, Sareban M, Schuler G, Thiele H, et al. Inflammation in Takotsubo cardiomyopathy: insights from cardiovascular magnetic resonance imaging. Eur Radiol 2010 Feb;20(2):422–31.

[66] Ueyama T, Hano T, Kasamatsu K, Yamamoto K, Tsuruo Y, Nishio I. Estrogen attenuates the emotional stress-induced cardiac responses in the animal model of Takotsubo (Ampulla) cardiomyopathy. J Cardiovasc Pharmacol 2003 Dec;42(Suppl. 1):S117–9.

[67] Ueyama T, Ishikura F, Matsuda A, Asanuma T, Ueda K, Ichinose M, et al. Chronic estrogen supplementation following ovariectomy improves the emotional stress-induced cardiovascular responses by indirect action on the nervous system and by direct action on the heart. Circ J 2007 Apr;71(4):565–73.

[68] Brenner R, Weilenmann D, Maeder MT, Jorg L, Bluzaite I, Rickli H, et al. Clinical characteristics, sex hormones, and long-term follow-up in Swiss postmenopausal women presenting with Takotsubo cardiomyopathy. Clin Cardiol 2012 Jun;35(6):340–7.

[69] Scantlebury DC, Prasad A, Rabinstein AA, Best PJ. Prevalence of migraine and Raynaud phenomenon in women with apical ballooning syndrome (Takotsubo or stress cardiomyopathy). Am J Cardiol 2013 May 1;111(9):1284–8.

[70] Salmoirago-Blotcher E, Dunsiger S, Swales HH, Aurigemma GP, Ockene I, Rosman L, et al. Reproductive history of women with Takotsubo cardiomyopathy. Am J Cardiol 2016 Dec 15;118(12):1922–8.

[71] Park SY, Kang JH, Jeong KJ, Lee J, Han JW, Choi WS, et al. Norepinephrine induces VEGF expression and angiogenesis by a hypoxia-inducible factor-1alpha protein-dependent mechanism. Int J Cancer 2011 May 15;128(10):2306–16.

[72] Santoro F, Ieva R, Ferraretti A, Fanelli M, Musaico F, Tarantino N, et al. Hemodynamic effects, safety, and feasibility of intravenous esmolol infusion during takotsubo cardiomyopathy with left ventricular outflow tract obstruction: results from a multicenter registry. Cardiovasc Ther 2016 Jun;34(3):161–6.

[73] Sharkey SW, Maron BJ. Epidemiology and clinical profile of Takotsubo cardiomyopathy. Circ J 2014;78(9):2119–28.

[74] Sharkey SW, Lesser JR, Zenovich AG, Maron MS, Lindberg J, Longe TF, et al. Acute and reversible cardiomyopathy provoked by stress in women from the United States. Circulation 2005 Feb 1;111(4):472–9.

[75] Sharkey SW, Pink VR, Lesser JR, Garberich RF, Maron MS, Maron BJ. Clinical profile of patients with high-risk Tako-Tsubo cardiomyopathy. Am J Cardiol 2015 Sep 1;116(5):765–72.

[76] Patel B, Assad D, Wiemann C, Zughaib M. Repeated use of albuterol inhaler as a potential cause of Takotsubo cardiomyopathy. Am J Case Rep 2014 May 19;15:221–5.

[77] Sherif K, Sehli S, Jenkins LA. Takotsubo cardiomyopathy after administration of norepinephrine. Proc (Bayl Univ Med Cent) 2016 Apr;29(2):166–7.