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Takotsubo cardiomyopathy – a clinical review

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Summary

Stress cardiomyopathy is characterised by reversible left ventricular dysfunction. It simulates an acute coronary syndrome (ACS), presenting with precordial pain or dyspnoea, changes of the ST segment, T wave, or QTc interval on electrocardiogram, and raised cardiac enzymes. Typical findings are disturbances of segmental contractility (apical hypokinesia or akinesia), with normal epicardial coronary arteries. The true prevalence is unknown, as the syndrome may be under-diagnosed; it is more common in postmenopausal women. There is usually a trigger in the form of physical or psychological stress. The electrocardiographic, echocardiographic, and ventriculographic changes resolve spontaneously over a variable period of time (from days to months). There are a number of pathophysiological theories, none of which has been shown to be definitive, suggesting that all of them may be involved to some extent. The prognosis is generally favourable, and recurrence is very rare.

key words: Takotsubo • left ventricular ballooning syndrome • stress cardiomyopathy • myocardial dysfunction

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DEFINITION, HISTORY, AND EPIDEMIOLOGY

Stress cardiomyopathy or Takotsubo syndrome (TS) is an acute, reversible disorder of the heart characterised by left ventricular dysfunction [1]. Its diagnosis continues to be controversial [1–8] (Table 1). The most widely accepted diagnostic criteria are those of the Mayo Clinic [5], which requires normality of the epicardial coronary arteries (Table 2). Other proposed diagnostic criteria admit non-significant coronary artery lesions [6] (Table 3) and, in the absence of coronary angiography, accept the results of echocardiography, cardiac magnetic resonance imaging, or isotope ventriculography [7] (Table 4). Kawai et al. [8] define this syndrome as a nosological entity in which there is acute ballooning of the apex of the left ventricle (LV) of unknown aetiology (Table 5).

The LV adopts the shape of a “takotsubo” (in Japanese, “tako” means octopus and “tsubo” means pot; takotsubo is the pot that Japanese fishermen use as an octopus trap). The syndrome receives this name because of the morphological similarity between this object (narrow neck and broad base with a globular form) and the LV during ventricular systole (on echocardiography and ventriculography) [9]. It is also known as ampulla cardiomyopathy, a name referring to the wide-bodied, narrow-necked container used in ancient Greece and Imperial Rome [8,10]. The morphology of the LV has led to a number of different names being used [8–20]. In general, to establish the diagnosis, it is accepted that other diseases of known aetiology (cerebrovascular pathology, pheochromocytoma, viral or idiopathic myocarditis, and epicardial ischemic disease) must be excluded [8].

In the 1990s, the Japanese authors Dote and Sato [21] were the first to describe this syndrome, calling it “takotsubo syndrome”. In 2001, Tsuchihashi et al. [15] published the first Japanese series, and the syndrome appeared as a new nosological entity. Since that time, case reports and series have been published [3,22–26] outside Asia [3,11,15,24,27], in African-American and white populations in the United States [25,28–32], in Europe [33–36], and in Oceania [37], excluding interracial, cultural, and geographic interactions. Due to the types of studies available, its true incidence is unknown, varying between 0.7% and 4.87% [25–38], although it may be under-diagnosed due to a lack of clinical suspicion [39–46].

It is more common in women (70–100% *vs.* 5–30% in men) [3,11–13,15,20–26,35,41–54], particularly in postmenopausal women (78–85.7%) [35,38]. Although it has been reported in younger patients, only 3% are under 50 years of age, and most of these are white individuals [30,34,35–55] and the mean age at onset is over 60 years [3,5,11,13,15,22–26,28,31,33,38–41,51,54–62]. A trigger in the form of a stressful event can usually be detected in 27–100% [15–17,33,48,51,64,65], and this could worsen the prognosis [60]; this event may be physical [3,17,33,42,46,64,65] or psychological [3,11,15,22,24,26,33,49,64–67]. The trigger is not related to sex, but whites appear to be more susceptible to emotional triggers than Asians [66]. In contrast, a stressful trigger is only found in about 3% of cases of ischemic cardiopathy [41]. There is no clear a risk factor associated with TS, though the most frequent association appears to be

Table 1. Abe and Kondo criteria.

<p>Major criteria:</p> <ul style="list-style-type: none"> – Reversible left ventricular ballooning with abnormalities of apical motility and hypercontractility of the basal segments. – Abnormalities of the ST segment/T wave on the ECG, simulating acute myocardial infarction.
<p>Minor criteria:</p> <ul style="list-style-type: none"> – Physical or emotional stress as triggering factors. – Limited elevation of the cardiac enzymes. – Precordial pain.
<p>Exclusion criteria:</p> <ul style="list-style-type: none"> – Ischaemic myocardial stunning. – Subarachnoid haemorrhage. – Pheochromocytoma crisis. – Acute myocarditis. – Tachycardia-induced cardiomyopathy.

Table 2. Diagnostic criteria of the Mayo Clinic.

<ul style="list-style-type: none"> – Suspicion of AMI based on precordial pain and ST elevation observed on the acute-phase ECG.
<ul style="list-style-type: none"> – Transient hypokinesia or akinesia of the middle and apical regions of the LV and functional hyperkinesia of the basal region, observed on ventriculography or echocardiography.
<ul style="list-style-type: none"> – Normal coronary arteries confirmed by arteriography (luminal narrowing of less than 50% in all the coronary arteries) in the first 24 hours after the onset of symptoms.
<ul style="list-style-type: none"> – Absence of recent significant head injury, intracranial haemorrhage, suspicion of pheochromocytoma, myocarditis, or hypertrophic cardiomyopathy.

Table 3. Prasad criteria.

<ul style="list-style-type: none"> – Transient hypokinesia, akinesia, or dyskinesia of the middle segments of the LV, with or without alterations at the apex. Regional abnormalities of wall motility extend in the area of distribution of a single epicardial vessel.
<ul style="list-style-type: none"> – Absence of an obstructed coronary artery or angiographic evidence of acute rupture of a plaque.
<ul style="list-style-type: none"> – New ECG abnormalities (ST elevation and/or T-wave inversion) or elevation of cardiac troponin.
<ul style="list-style-type: none"> – Absence of: <ul style="list-style-type: none"> Recent head injury Intracranial haemorrhage Pheochromocytoma Myocarditis Hypertrophic cardiomyopathy

systemic hypertension (13–80%), followed by hyperlipidemia (0–60%), diabetes mellitus (0–33%), smoking (0–50%), and a family history of cardiovascular disease (0–50%) [3,11,15,22,24,26,33,49,64–66,68].

Table 4. Segovia Cubero criteria.

<p>Previous conditions (both obligatory):</p> <ol style="list-style-type: none"> 1. Evidence of a transient apical dysfunction of the LV with the typical form in systole (rounded apex with narrow neck due to hypercontractility of the basal segments), diagnosed by angiography, echocardiography, isotope scans, or cardiac magnetic resonance imaging. The disturbance typically reverts in 2–3 weeks, although it can persist for up to 2 months. 2. Absence of other conditions associated with regional transient systolic dysfunction of the LV: subarachnoid haemorrhage, phaeochromocytoma, ischaemic myocardial stunning, drugs (cocaine), myocarditis, etc.
<p>Diagnostic criteria:</p> <ol style="list-style-type: none"> 1. Major: Early coronary angiography (within the first 24 h) showing no anatomical lesions. 2. Minor: <ul style="list-style-type: none"> • Early coronary angiography showing non-significant lesions (less than 50% without characteristics of a complicated plaque or intraluminal thrombus). • Late coronary angiography (from the second to the seventh day after the onset of the syndrome) showing no significant lesions. • Physical or psychological stress as the trigger of the disorder. • Typical ECG changes: <ul style="list-style-type: none"> • ST segment elevation in the acute phase, more marked in V4–V6 than in V1–V3. • Appearance of Q waves that disappear after the acute phase. • Very prominent negative T waves in V1–V6. • QTc prolongation. • Woman over 50 years of age.
<p>Confirmed TADS: major criterion or 2 or more minor criteria, including an angiographic criterion. Probable TADS: 2 or more minor criteria, with no angiographic criterion. TADS: transient apical dysfunction syndrome.</p>

Table 5. Kawai criteria.

<p>Exclusion criteria:</p> <ol style="list-style-type: none"> 1. Significant organic stenosis or spasm of a coronary artery. In particular, AMI due to a lesion of the anterior descending artery of the left coronary artery, which irrigates a large territory including the apex of the LV (urgent coronary angiography is desirable in order to view the image in the acute phase; during the chronic phase, coronary angiography is necessary to confirm the presence or absence of significant stenotic lesions or abnormal lesions that could explain the ventricular contraction). 2. Cerebrovascular disturbances. 3. Phaeochromocytoma. 4. Viral or idiopathic myocarditis. <p>(Note: Coronary angiography is required for the exclusion of coronary artery lesions. Takotsubo-like myocardial dysfunction can occur in conditions such as cerebrovascular disorders or phaeochromocytoma).</p>
<p>Diagnostic references:</p> <ol style="list-style-type: none"> 1. Symptoms: Precordial pain and dyspnoea similar to the findings in the acute coronary syndrome. Takotsubo cardiomyopathy can also occur without symptoms. 2. Triggers: Emotional or physical stress, although it can also occur without any obvious trigger. 3. Age and gender: There is a recognized tendency to a higher frequency in elderly individuals, principally women. 4. Ventricular morphology: Apical ballooning with rapid recovery on ventriculography and echocardiography. 5. ECG: ST elevation may be observed immediately after the event. T waves progressively become negative in various leads and the QT interval progressively lengthens. These changes gradually improve, but the T waves may remain negative for months. Pathological Q waves and alterations of the QRS voltage may be observed in the acute phase. 6. Cardiac biomarkers: There is only a slight rise in the cardiac enzymes and troponin. 7. Nuclear medicine scan of the heart: Abnormalities may be detected on myocardial gamma scan in some cases. 8. Prognosis: Recovery is rapid in most cases, but some patients develop acute pulmonary oedema and other sequelae, even death.

CLINICAL PRESENTATION AND COMPLICATIONS

Although the syndrome may initially be asymptomatic (2–20%) [27,48], the clinical presentation is usually similar to an acute coronary syndrome. The most common symptom is precordial pain [6,7,34,69], although this may be atypical; it is reported in 50–100% of cases at onset [3,5,15,22–26,33–36,48,50,51,64–66,68,69] and is more

common in whites [66]. African-Americans more commonly present with respiratory insufficiency [31]. Other presentations include abdominal symptoms (8–10%) [32,34,41,65], myalgia (0.5–3.33%) [24,27,66], dyspnea (7–60%) [6,15,31,32–36,48,64–68], palpitations (5–9%) [66], presyncope or syncope [6–22%], usually associated with an arrhythmia [5,13,21,32–36,42,46,49,50,70], or even cardiorespiratory arrest (0.5–8%) or sudden death (3%)

[70,71]. Heart failure is a common form of onset of the syndrome (11–28%), presenting as acute pulmonary edema (3–50%) [5,6,15,35,48,65,66,68,69] or cardiogenic shock (2–46%) [6,15,16,21–26,31,32,35,36,46,53,72,73]. It was erroneously initially attributed to respiratory insufficiency (7–69%) due to a respiratory exacerbation of chronic obstructive pulmonary disease, pneumonia, or even respiratory distress [6,12,22,31,32,66,74–77].

All types of arrhythmias have been reported, with a very variable incidence (estimated frequency, 5.7%, which could be lower with beta-blockers); the most common arrhythmia is probably extrasystoles [78]. These arrhythmias, and the conduction blocks in particular, are usually transitory, and the prognosis appears to depend more on the degree of ventricular dysfunction than on the arrhythmia [79]. The causes of these arrhythmias are unknown, and a number of theories have been proposed. Furushima et al. [80], through electrophysiological study of an ST with a long QTc interval and torsade de pointes, which recurred after normalisation of the echocardiographic and electrocardiographic disturbances, observed changes in the myocardial-epicardial repolarisation gradients of the LV. Fisher et al. [81], using magnetic mapping by cardiac magnetic resonance, observed lesions similar to myocarditis or ischemia, and disturbances of repolarisation that persisted for longer than the structural changes (more than 6–12 months). When the arrhythmias develop during the resolution phase, they suggest that normalisation of ventricular function depends on a slow electric remodelling; this would explain recurrence of the arrhythmias and the high risk of sudden death despite complete recovery of the electrocardiographic and echocardiographic changes [82–88].

Other, rarer complications have been reported, such as pneumothorax (0.5–8.3%) [46,66], pericarditis in the subacute [29] or recovery [89], phases of the syndrome, and mechanical complications such as rupture of the free wall of the LV (0.5%) [5,66,90–93], perforation of the interventricular septum (0.5%) [66], or rupture of the papillary muscles [94].

The area of dyskinesia may give rise to intracavity thrombi, with an incidence of 2.5–9%; the thrombi are usually found at the apex, and thromboembolic phenomena have been reported in 0.8–14% of cases of TS [5,25,34,93,95].

THE ELECTROCARDIOGRAM

Although the initial electrocardiogram (ECG) may be non-specific or normal, the majority (11–100%) present elevation of the ST segment, particularly affecting the anterior wall (36–100%) and, more rarely, the inferior or lateral walls (4–50% and 5–70%, respectively) or in aVR [3,6,7,13,15,21–26,33–36,50,54,64–66,70,96–99]; ST segment depression has been reported in 6–23% [13,64]. These changes may be very dynamic [98,99]. An absence of R-wave progression in the anterior wall may also be seen (7–32%) [17,22]. T wave inversion is very common (17–100%) [7,13,15,21,33–36,64,66,96–98], and may be associated with a poorer prognosis [62,98]; however, peaked T waves sometimes predominate (86%) [64,98]. A long QTc interval is seen in 50–100% [3,7,12,21–26,64]. Pathological Q waves are observed in 20–63% [6,7,15,21–26,33–44,64]

and new bundle branch blocks develop in approximately 6–8% [5,21–25]. Racial differences exist in the electrocardiographic changes, with a higher frequency of inverted T waves in whites, and a higher incidence of ST elevation in Asians [64]; in blacks the initial ECG is more commonly normal, with a rapid progression to T wave inversion and a prolonged QTc interval [31]. The course of the changes [17,25,36,62,64,96–98] usually shows ST elevation or depression for 1 to 2 days, and there may even be new intraventricular conduction disturbances [6,17,25,36]. In the subacute phase, the ST changes normalise and disturbances of the QTc interval develop but disappear rapidly; T wave inversion develops in parallel with lengthening of the QTc interval but is of longer duration (1–4 months) [15,36]. Pathological Q waves (myocardial stunning) may be observed in the chronic phase, but disappear more rapidly than in cardiac ischemia, although they may persist indefinitely in 10% of cases [24].

T wave inversion and the long QTc interval persist after normalisation of the echocardiographic images, whereas R wave progression normalises in parallel with the improvement in motility [17]. All these electrocardiographic changes usually resolve within 3 weeks to 1 year [3,13,17,22,25,33,36,51,62,64,96–98].

Unsuccessful attempts have been made to differentiate TS from ACS based on ECG findings [56,91,100–104]. Ogura et al. [101] and Segovia Cubero et al. [7] observed that there are fewer pathological Q waves, a longer QTc segment, less ST depression and a higher V4-V6 to V1-V3 ratio of ST elevation in TS; they considered that an ST segment with a V4-V6/V1-V3 ratio greater than 1 had a high sensitivity and specificity for TS. Other authors observed that ST elevation is greater in patients with myocardial infarction [102–104], whereas ST elevation of less than 1.75 mm in V2 or less than 2.5 mm in V3 is more specific to TS [103].

CARDIAC BIOMARKERS

Although no elevation of the biomarkers has been reported in about 5% of cases of this syndrome [14,25,64], there is typically a slight increase in the creatine kinase MB and in troponins I and T, although at lower levels than occur with acute myocardial infarction [5,15,21,33,36,37,41,64,66,102–104]. The echocardiographic, ventriculographic, and even electrocardiographic changes usually indicate severe cardiac disturbances, but these are not reflected in the enzyme levels, which are closer to values found in conditions such as myopericarditis or the non-ischemic cardiomyopathies [97,105]. At the present time, the cut-off point for the enzyme levels to differentiate between TS and ACS remains to be defined [106]; however, the majority of authors have not found increases of the cTnI of over 4.5 ng/ml or of CPK-MB of over 10.5 U/L, and higher values are usually suggestive of ischemia [106].

Measurement has also been performed of the plasma levels of brain natriuretic peptide (BNP) [106–109] and NT-proBNP [110], which have been correlated with the degree of cardiac failure and the fall in left ventricular ejection fraction (LVEF), although their correlation with survival is not known.

There is no evidence of a rise in catecholamines in 30% of patients in the acute phase [33,111]. When there is a rise

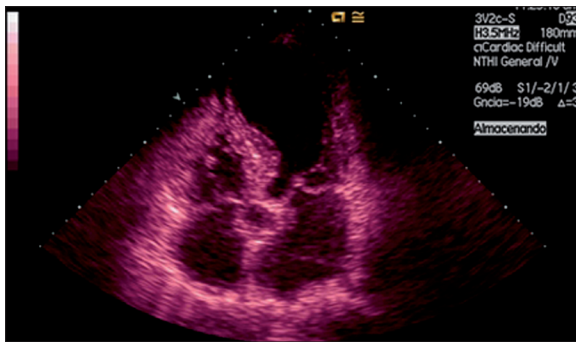


Figure 1. Echocardiographic image in apical ballooning which is also observed mitral prolapse (P2).

above normal, it is very marked [46] for several weeks and falls progressively. Elevation of C-reactive protein (CRP) is detected in 50% of patients and is a sign of poor prognosis and predictor of mortality [36,64,112] in TS.

ECHOCARDIOGRAPHY

The typical finding is of apical ballooning of the left ventricle. This is due to akinesia, hypokinesia, or dyskinesia of the apical and middle segments of the LV and hyperkinesia of the basal segments [8,24,28] (Figure 1). Some disturbances of contractility are similar to those that occur in systemic hypertension due to an increase in afterload [113]. The LVEF is low or very low from the initial phase, with values below 30% in some cases [16,23,26,32,105] and up to 75% [64]. In the subacute phase, global and segmental systolic function and the electrocardiographic changes improve over a period of days, weeks, or a few months, until they stabilise with an LVEF above 50% [5,11,15,16,21–24,56–69,114–119]. In general, echocardiography is normal at 1 year [7,14,21–24]; the rate of recovery is more rapid in Asians than in whites [120].

Despite this, there is a noticeable lack of use of quantitative echocardiographic techniques such as the strain, strain rate, or velocity vector imaging for the diagnosis and follow-up of these patients [121,122] (Figure 2). The descriptions of diastolic function mainly use transmitral flow [123], and ignore information from the pulmonary veins or from tissue Doppler studies, and the diastolic dysfunction detected could be spurious. Furthermore, little use has been made of intravenous echocardiographic contrast, which has enabled intraventricular thrombi [34] and abnormalities of the coronary microcirculation to be detected, or dobutamine echocardiography, which can reveal underlying dysfunction [123].

Changes in the LVEF are initially similar to those seen in ischemic heart disease, although recovery is better in patients with TS than in those with ACS [41]. Functional valve disturbances can also develop, including: 1) mild-moderate tricuspid regurgitation (50%) [54] associated with pulmonary hypertension (mean pulmonary arterial pressure 46.6 ± 10.5 mmHg) [54] in 33%; 2) mild-moderate aortic insufficiency (12.5%) [54]; and 3) mitral insufficiency of grade 2 or higher, present in 9.7–62.5% [31,41]. Systolic anterior movement may be observed (6.67%) [54] and a gradient in the LV outflow tract (43–100 mmHg) (20–35.71%)

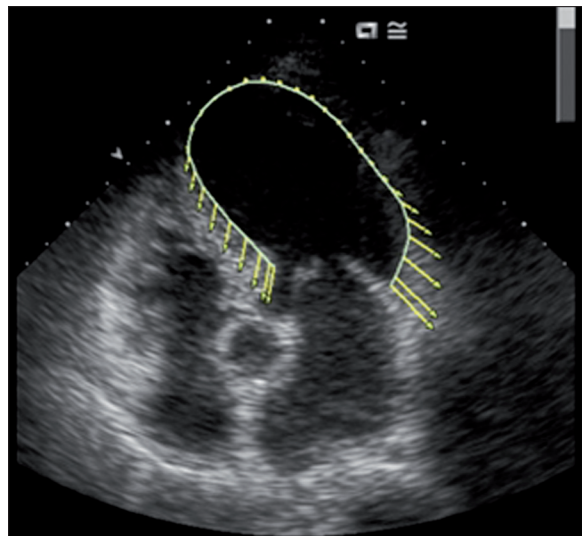


Figure 2. This is hybrid speckle tracking image of takotsubo patient. There is a pathological displacement curve in the apical segments and increased in the basal segments.

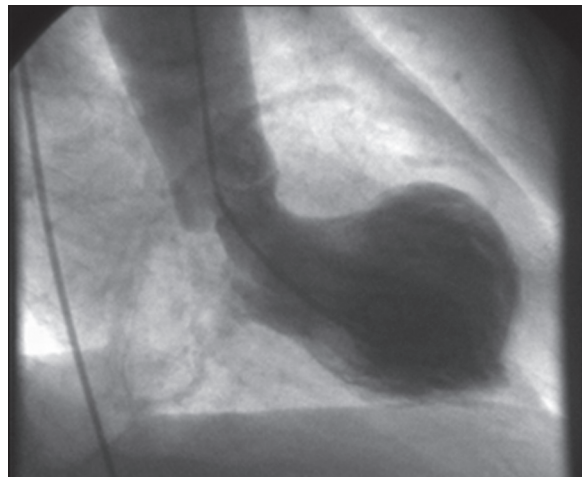


Figure 3. Ventriculography image of apical ballooning which shows apical akinesia and basal hyperkinesis.

[54,68]. These findings are usually associated with a Killip III-IV infarct (50%) and higher levels of cardiac enzymes [68]. Mitral insufficiency leads to a lower LVEF and a slow ventricular recovery (79%) [68], with complete recovery of the syndrome occurring at around 6 months, although 8.1% continue to present mitral insufficiency of grade 2/4 or higher [124]. Severe mitral insufficiency is a cause of death in 14.29% [68]. Tricuspid insufficiency reverts and the pulmonary hypertension disappears in 13.33% [54].

CATHETERISATION

Normality of the epicardial coronary arteries is normally a requirement for the diagnosis of TS [4,7,13,74]. Overall, it is considered that the number of vessels affected in TS is zero compared to 1.6 ± 0.7 in ACS; however, other authors have found stenoses not greater than 50% in 10–21% [21], or even greater than 50% [5,34,125]. Some coronary artery lesions have a chronic morphology with no angiographic

evidence of acute complication by virtue of its prevalence in the population at risk, whereas others are acute lesions giving rise to ischemia associated with the TS [95,125]. Angiography has revealed spontaneous coronary artery spasm in 1.4–10% [25,94,126], induced spasm in 4.5–71% [3,11,13] and vasoconstriction in 21–100% [3,21]. Asian individuals are more likely to develop vasospasm, but this likelihood may be due to the widespread use of provocation tests in Japan [127]. Ventriculography shows the same changes as echocardiography (Figure 3).

The TIMI frame count is higher in TS [2,3,21,22,34,128], which may be caused by diffuse coronary microvascular dysfunction, although it usually normalises after functional recovery [2].

Angiographic blush is present in two-thirds of patients at onset of the syndrome, and the severity is determined by the magnitude of the rise in the troponin levels and by the ECG changes [48,97]. This leads us to question whether TS is a distinct entity or is a stage of ischemia [129,130].

IMAGING STUDIES

Multislice computed tomography (mCT) and cardiac magnetic resonance imaging (cMRI) are also useful in the diagnosis of apical ballooning. mCT is a non-invasive test that is suitable for the differential diagnosis between infarction and TS, showing not only the coronary artery circulation and its lesions, but also disturbances of cardiac contractility. According to cMRI, the myocardium initially affected is viable [131]. Delayed enhancement with gadolinium is usually present in myocarditis and ACS [2,25,132] and does not occur in 95% of patients with TS. However, cases of TS with delayed gadolinium uptake have been reported [133], giving rise to doubts of ischemia. Myocardial SPECT reveals a fall in technetium-99m tetrofosmin uptake in the acute phase, indicative of a decrease in myocardial perfusion [100,135,136]. Reversible alterations of a number of radioactive tracers, such as ¹²³I-BMIPP and ¹²³I-MIBG, could indicate a reduction in fatty acid and glucose metabolism, alterations of coronary microcirculation, or a possible imbalance in the sympathetic innervation between the apical and basal regions [137].

BIOPSY

There is no specific histopathological pattern in TS. Focal lesions of myocytolysis are usually observed, with a reduction in the number of myocytes and a polymorphonuclear infiltrate with fibrosis [3,11,24,27]. However, there is controversy over the findings in the acute phase, with an inflammatory infiltrate [43] or myocyte necrosis [33] being found. Wittstein et al. [26] described bands of necrotic contraction without myocyte necrosis, similar to that observed in patients who die in tragic circumstances and in patients with catecholamine-induced cardiomyopathy [2,26], although these changes have also been observed in patients without inotropes and with no increase in the catecholamines [104]. Fatty infiltration of the myocardium or cardiac steatosis suggests focal damage [37,78,112,121] due to metabolic changes that can progress to a cardiomyopathy that usually precedes ventricular systolic dysfunction, as occurs in patients with type 2 diabetes mellitus. Rather than its myocardial distribution,

the characteristics of the fat are similar to the infiltration in arrhythmogenic dysplasia [22], making it necessary to include this disorder in the differential diagnosis. Few biopsies of the LV are performed and, although the results are not specific, it does appear that there is an increased accumulation of periodic acid-Schiff-positive material, suggestive of myocardial hibernation [121].

AETIOLOGY AND PATHOGENESIS

The aetiology and pathogenesis of this disorder are unknown. One theory is the possible existence of myocardial stunning secondary to a primary metabolic disturbance characterized by dysfunctional metabolism of cardiomyocytes [138], affecting either glucose [139] or fatty acid metabolism, or due to mitochondrial disturbances [140–142]. Another possibility is stress-induced catecholamine release, producing cardiac stunning [143,144] through a direct lesion of the myocytes and vasoconstriction [24] secondary to increased calcium [142], which activates cAMP, causing damage to the cardiac cells and favouring free radical release. The apical region is the most vulnerable area due to the large number of adrenergic receptors [144]. Structurally, the third layer of the myocardial architecture is absent at the apex, and this region presents a rapid loss of elasticity after excessive dilatation. It is also more susceptible to developing ischemia due to a precarious coronary blood flow, as it is in a borderline region of the coronary circulation [18]. Segmental alterations of contractility may be due to the local release of catecholamines in this frontier region [145]. There are fewer sympathetic terminals in the base of the heart than at the apex; this makes the apex more vulnerable to a rapid rise in catecholamine levels and means that the apical myocardium has an increased response to sympathetic stimulation. In situations of stress, functional and/or structural differences in regional coronary blood flow may develop due to an alteration in the apex-base perfusion gradient, with a deficit developing at the apex [146].

Due to the oestrogen deficit, women in the perimenopausal and postmenopausal period have a higher risk of developing angina due to microvascular dysfunction associated with normal coronary arteries; this is caused by the influence of these hormones on the sympathetic system [147]. In a situation of stress, men release a larger quantity of catecholamines and are more sensitive to vasoconstriction; however, women are more vulnerable to sympathetic mediators, present more episodes of angina, and develop more marked disturbances of cardiac contractility and of LVEF [148,149]. However, it appears that a lack of oestrogens could be a primary cause of TS due to an indirect action on the nervous system or a direct action on the heart [150].

Peripheral endothelial function and microvascular function have been studied in the acute phase of TS, and no dysfunctions have been observed [151]. Another hypothesis that has been proposed is spasm of the epicardial arteries. It appears unlikely that the left ventricular dysfunction that occurs in this syndrome could be due only to coronary artery spasm. The disorder of motility affects the territories of the 3 coronary arteries. One possibility could be spasm of all the arteries at the same time [3,24,34], or vasoconstriction due to an increase in sympathetic tone caused by the stress, and that this provokes microvascular dysfunction [21,142].

Acute myocarditis forms part of the differential diagnosis [3,11,13,24,27], a theory based on the fact that in some cases positive results for viruses have been found in biopsies and serological tests [34,152]; however, there is no microbiological agent related with TS.

The pathogenesis of the dynamic gradient that may be detected in TS could be due to a geometric susceptibility of the heart – a sigmoid or bulging interventricular septum, a small LV [35,153–155], or abnormal mitro-aortic and sep-to-aortic angles [156]. Elderly women have a greater tendency to develop hypertrophy of the basal anterior septum. The angle of the septum is responsible for the increase in the speed in the outflow tract and simulates a hypertrophic cardiomyopathy [157]. It is also associated with an abnormal orientation of the mitral valve due to flaccidity, deformity of the mitral valve, false chordae, disturbances of the papillary muscles, or systolic anterior movement [158–160]; more rarely the obstruction is secondary to hyperdynamic contraction of the basal segments of the LV. The onset of symptoms usually occurs in the context of hypovolemia or major adrenergic stimuli. In some circumstances, the dynamic obstruction precedes apical ballooning, and has a good prognosis [35,155,160].

Ibañez et al. [161] used intravascular ultrasound (IVUS) to study the left anterior descending artery in patients with TS and found that all had unstable atheromatous plaques with the possibility of early spontaneous reperfusion. The duration of ischemia was short and the myocardial damage gave rise only to a small elevation of the enzymes; left ventricular dysfunction was due to stunning. This spontaneous lysis of the thrombus left the coronary arteries with a normal angiographic appearance. Another hypothesis by Ibañez et al. [162] is of a susceptible coronary vascular tree, as in the case of recurrent epicardial arteries. These abnormalities have also been described by other authors, with an incidence of 72–92% in normal hearts [3,5,162].

Another theory is the genetic basis [63,163]. Phenotypically, Mediterranean and Asian women, due to their constitutions and the presence of hypoplastic apical epicardial arteries, have a greater susceptibility to this dysfunction. However, genetic analyses have not identified a mutation or polymorphism [164].

ATYPICAL FORMS

At the present time, one-third of patients are reported to present a variant form of the disorder [130]. One of the most important variants is inverted takotsubo [17,40,50,52,58,60,76,165,166,170], which Bonnemeier called artichoke heart [171]; the apex is hypercontractile and the basal segments are akinetic. Aubert et al. [172] described transient midventricular ballooning [30] or hawk's beak [173], with movement of the apex and basal segments and akinesia of the middle region. Reuss et al. [174] described apical akinesia with normal midventricular movement and apical hypercontractility. Kim et al. [175] described basal akinesia, normal midventricular movement, and basal hypokinesia (Table 6) [2]. Midventricular disorders are detected in 7–40% of cases, with 5% in the inverse syndrome and 7% in the other forms [40,166].

The origin of these differences is unclear. It may be due to a variation in autonomic innervation and/or in the

Table 6. Atypical forms of Takotsubo.

Type I. Takotsubo cardiomyopathy with apical ballooning.
Type II. Midventricular ballooning.
Type III. Cardiomyopathy with apical hypercontractility.
Type IV. Basal ballooning.
Type V. Involvement of other segments.

distribution of adrenergic receptors within the heart due to an irregular subendocardial model [30,58]. It is thought that apical hypercontractility is due to a reduction in the density of synaptic terminals in the apex or that, after the akinesia, the apex is the first area to show a functional recovery after a major, initially global disorder [38]. The possibility of a migratory TS has also been proposed, in which apical hypercontractility constitutes one of the periods of a single syndrome [165]. Rupture of an atheromatous plaque cannot itself explain the variants [58,59,130]. Compared to classic TS, variant TS is more common in premenopausal and younger women [166], and there is greater preservation of the LEVF [166]. The atypical forms are associated with fewer risk factors, less T wave inversion, lower enzyme levels, and a rapid recovery from the dysfunction [166]. The midventricular form presents more Q waves and more hypotension than typical TS, which is associated initially with a greater degree of cardiogenic shock and heart failure [167]. Cardiac magnetic resonance imaging reveals greater involvement of segments 1–12 in the atypical forms and of segments 7–17 in the classic form [58]. There are no differences in the TIMI between the classic and midventricular forms [166], and there are also no differences in improvement [58].

BIVENTRICULAR INVOLVEMENT

Nyui et al. [168] were the first to describe TS with right ventricular dysfunction, and this has subsequently been corroborated by other authors [5,43,54,64,169–172]. There are no clinical differences in these patients [130,169], but there is a greater degree of systolic dysfunction and heart failure [170,172], greater dilatation of the right ventricle (RV), greater involvement of the lateral and inferior segments [172], more marked pleural effusion [172], a greater need for hemodynamic support and cardiopulmonary resuscitation [129], and a longer hospital stay [129]. Severe right apical dysfunction due to hypokinesia occurs in 14.29% of cases. Biventricular involvement is present in 26–40% of cases [130,169,171,172].

Disturbances of contractility in the right-sided cavities may be indistinguishable from those present in chronic or acute diseases such as pulmonary thromboembolism (inverted McConnell sign) [171], and there is early apical akinesia [28]. The mechanisms implicated in right-sided dysfunction are probably related to catecholamines.

TREATMENT

A correct diagnosis will avoid treatment of ischemic heart disease [25], which has not been shown to be of any benefit in TS and could give rise to adverse effects [7,18]. At the present time, treatment is symptomatic and, as with other

cardiomyopathies, is determined by the complications occurring during the acute phase [20–29,56].

The use of intra-aortic balloon pump (IABP) support has been required [31,35,56], and even cardiopulmonary support techniques and renal replacement therapy such as continuous venovenous hemodiafiltration. The use of inotropes is controversial due to the increase in circulating catecholamines [25]. Levosimendan [88,173] may be beneficial for its inotropic and vasodilator effects. IABP is required by 8–46% of patients, less than in the ACS [41]. Up to 36.36% of patients require vasoactive drugs [35,54], and inotropes are used in 20–43.75% [15,21]. Short-term anticoagulation may be considered, at least until recovery of ventricular function. The implantation of defibrillators is controversial; they are implanted in 2.5–8.3% of cases [46,50], but the number of arrhythmogenic events registered after a year of follow-up could be zero [70].

In the case of left ventricular outflow obstruction with hemodynamic repercussion, treatment should be given with beta-blockers, alpha-adrenergic agents such as phenylephrine, and volume expansion; calcium channel blockers may be used to reduce the outflow gradient. Most important in these cases is to treat the trigger and to recognise the condition in order to avoid treatment with nitrites or inotropes [152–160,167]. The use of calcium channel blockers such as diltiazem or verapamil may be indicated if vasospasm is suspected [161]. In the case of functional mitral insufficiency, initial treatment may be conservative; 36% require IABP and valve replacement may even be necessary [68].

Long-term treatment is currently undefined [40]. It is thought that it may be appropriate in order to reduce myocardial stunning caused by catecholamines and that it would theoretically avoid recurrences. However, there is no evidence to support the use of chronic pharmacological treatment except in cases of cardiac dysfunction, despite the fact that treatment could alter the incidence of recurrence [25,174]. Experimental studies are evaluating the controversial benefit of oestradiol [175], ranolazine [176], and the reduction in the frequency of recurrence through the administration of beta-blockers [177], but beta-blocking drugs were not absolutely protective [178].

CRITICAL CARE MEDICINE AND TAKOTSUBO SYNDROME

In 28% of cases, the apical ballooning syndrome develops in critically ill patients with no primary heart disease [179,180], but there are few studies on this subject due to a lack of diagnosis [2]. The situation of stress to which the critically ill patient is subjected acts as a trigger. Park et al. [179] studied 92 patients admitted to an intensive care unit and, through the use of echocardiography at the time of admission, with repetition a few days later, observed that 28% of patients presented echocardiographic abnormalities compatible with TS, with a reduction of the LVEF, and sepsis as the variable associated with cardiac dysfunction. This phenomenon has also been observed in critically ill patients with other diseases [36] and even after cardiopulmonary resuscitation [181]; these patients present echocardiographic signs of myocardial dysfunction, with an initially reduced LVEF that improves over time, as do the electrocardiographic disturbances. Haghi et al. [180] included 6

patients with a diagnosis of TS. All the patients presented electrocardiographic and echocardiographic disturbances with an initially reduced LVEF and normal angiography.

The true prevalence is unknown. The age is similar to that of patients outside intensive care units (63–68 years). Only 35–50% are women [36]. Clinically, the typical symptoms are not usually present, possibly due to the state of sedation-analgesia under which these patients are usually maintained, or due to the hemodynamic situation or severity of the critically ill patients. Occasionally patients refer precordial discomfort [180], although they are more likely to present pulmonary edema, ischemic changes on the ECG, sometimes detected by telemetry, arrhythmias such as ventricular tachycardia, a moderate rise in the biomarkers, or hemodynamic disturbances. The most prevalent risk factor is systemic hypertension [36]. The echocardiographic, electrocardiographic, and enzyme changes normalise over a period that varies between 1 and 6 months [36,179–181]. Mortality is somewhat lower: 16.67–52% [48,51,52], with higher figures than in patients not admitted to these units; the cardiac dysfunction possibly affects the prognosis. There is a growing need for vasoactive drugs [180]: 54.55–83.33% [36,180,181]. The etiology and pathogenesis are believed to be similar to other forms of TS [36,180,181].

The differential diagnosis must be made with stress cardiomyopathies (of the critically ill patient, catecholamine-induced, neurological, and various respiratory insufficiencies) [2,182]. The cardiac dysfunction that develops could be an expression of a previous disease or the intercurrent situation that the patient is suffering (Table 7), or procedures that the patient requires during admission to the intensive care unit (endotracheal intubation, mechanical ventilation, tracheostomy, etc), and not a true TS. The problem is in differentiating whether the disorder is due to the patient's underlying disease, is a TS, or if the 2 are the same thing. The end result is that the association with cardiac dysfunction can worsen the prognosis. Clinically, the subtlety of the initial symptoms, the lack of suspicion, and the low level of use of bedside echocardiography, means that diagnosis will be delayed and that treatments may be used erroneously and, on occasions, even with a risk of causing harm [36].

PROGNOSIS AND RECURRENCE

Complications are estimated to occur in 18.9% of cases of TS, with no racial differences [66]. Mortality varies between 0% and 12% [5,6,13,15,22,25,32,35]. There are no long-term studies that provide approximate figures. Tsuchihashi et al. [15] estimate in-hospital mortality at 1%, and mortality at 1 year of follow-up that reaches 2%. Donahue et al. [66] observed that older patients die earlier and that whites had a higher mortality than Asians (6% *vs.* 1.7%). Parodi et al. [68] detected a higher mortality among coronary patients (14% *vs.* 3%). Nuñez-Gil et al. [124] did not observe any in-hospital deaths, but they did detect a mortality of 3.2% during follow-up (35 months), although these figures are lower than for ACS (hospital mortality: 6.5%; mortality during follow-up for 35 months: 17.2%). Other authors have not analysed mortality in their studies [21,24,26,42]. Morbidity and mortality are lower in TS patients than in patients with ACS, and left ventricular function could determine the prognosis [21,42,60].

Table 7. Cardiac dysfunction.

Structural cardiomyopathies:	
1.	Non-compaction
2.	Hypertrophic
3.	Dilated
4.	Arrhythmogenic
Acquired cardiomyopathies:	
1.	Critically ill patient
2.	Peri-partum cardiomyopathy
3.	Catecholaminergic: Pheochromocytoma Paraganglioma
4.	Endocrinological: Hyper/hypothyroidism/Thyrotoxicosis Addison's disease/Adrenal insufficiency Hyperparathyroidism Anorexia nervosa Diabetes Hypertension/Hypotension Hyponatraemia
5.	Autoimmune/Collagen diseases: SLE Rheumatoid arthritis Scleroderma PAN Dermatomyositis Myasthenia gravis Vasculitis
6.	Respiratory disease: COPD Asthma Pulmonary embolism Pneumothorax Cardiorespiratory arrest Smoke inhalation
7.	Neurological disease: Ischaemic/haemorrhagic stroke TIA Subarachnoid haemorrhage Head injury Status epilepticus Surgery for cerebral tumours Neuromuscular diseases Neuroleptic malignant syndrome
8.	Drug abuse: Cocaine Opiates Alcohol
9.	Cardiological procedures: Stress test Electrophysiological Pneumopericardium
10.	Renal procedures: Haemodialysis
11.	Anaphylactic disorders
12.	Transplants: Liver
13.	Drugs: Corticosteroids Chemotherapeutic agents Immunosuppressants Antiarrhythmic agents
14.	Anaesthetic procedures and different types of surgery: Thoracic surgery Cardiac surgery Implantation of a permanent pacemaker
15.	Infectious: Endocarditis/myocarditis Sepsis
16.	Tumours

Recurrence is rare but has been reported [63,74]. Clinically, the syndrome reappears as precordial pain and, morphologically, can vary in the type of echocardiographic or ventriculographic presentation [74]. The time to recurrence varies

between 3 months and 13 years [15,21,25,63]. The incidence does not exceed 13% [2,5,6,15,21–25,66,68,124,185] and, as a rule, recurrence is not observed [3,11,33,36,64,68,78,89,129]. There is also doubt about whether all recurrences are TS [183]. At the present time, reasonable doubt may still be expressed about the complete reversibility of a stress cardiomyopathy [184,186].

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