SMGroup

Tako-Tsubo Syndrome

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ABSTRACT

Tako-Tsubo Syndrome **(TTS),** also known as "Broken-Heart Syndrome", "Apical Ballooning Syndrome" or "Stress Cardiomyopathy", is an emerging clinical syndrome characterized by acute left ventricular dysfunction that mimics an acute coronary syndrome in regard to clinical presentation and non-invasive instrumental findings. TTS affects more commonly postmenopausal women (female-to-male ratio 9:1) and it is usually triggered by a physical or emotional stress.

While clinical presentation and electrocardiographic findings resemble an acute coronary syndrome, coronary angiography usually shows normal or near-normal coronary arteries.

Typically, apical and mid left ventricular dysfunction in TTS is transient resulting in a progressive improvement and normalization of LV function over 3-12 weeks.

The pathophysiology of TTS is controversial, but the common final pathway is represented by transient microvascular vasoconstriction of the dysfunctional myocardial regions.

Although TTS was initially considered a relatively benign disease, it has been recently reported a high complications rate accounting for 50% of patients with 2-5% of in-hospital mortality rate. Thus, a careful clinical monitoring of TTS patients is recommended in the acute phase of disease in order to detect and treat complications such as acute heart failure, arrhythmias, intra-cardiac thrombus or embolic events. Additionally, a long-term clinical management of TTS is also recommended to monitor clinical and instrumental improvement of heart function.

Since no large randomized studies are available about TTS patients, the therapy is empirical and based on clinical judgement and opinion of experts. Thus, several advances about TTS are actually to reach.

Keywords: Tako-Tsubo Syndrome; Heart failure; Acute coronary syndrome; Acute microvascular dysfunction

Abbreviation: TTS: Tako-Tsubo Syndrome; ECG: ElectroCardioGram

INTRODUCTION

Tako-Tsubo Syndrome **(TTS),** also known as "Broken-Heart syndrome", "Apical Ballooning Syndrome" or "Stress Cardiomyopathy", is an acquired transient disease characterized by acute systolic and diastolic left ventricular dysfunction, usually triggered by a physical or emotional stress.

The first description of TTS was made in 1990 by a japanese group [1], which introduced the term "tako-tsubo" (a peculiar japanese octopus pot with a round bottomed and narrow neck) to describe the characteristic shape of the left ventricle in this pathological condition [figure 1]. Since then, a large number of cases have been identified in North America, Europe, Asia and Australia, showing a pandemic distribution.
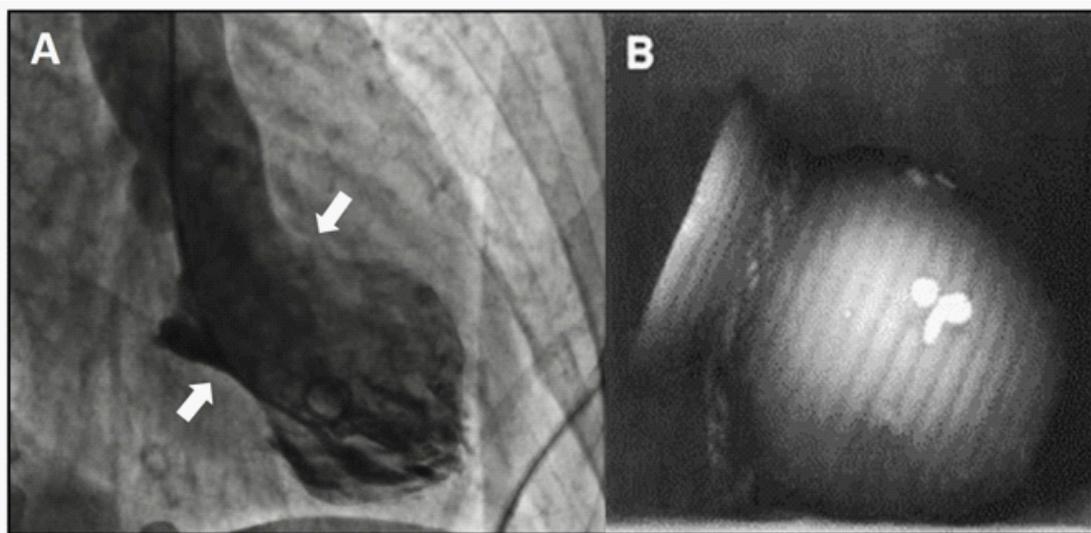

Figure 1: The japanese term tako tsubo refers to a pot used for catching octopuses and suggests the aspect assumed by the left ventricle during the systole due to the typical regional wall motion abnormalities.

EPIDEMIOLOGY

Nowadays, the real incidence of TTS is unknown due to the lack of reliable epidemiological data. Moreover, several studies had suggested that 1-2% of patients admitted to hospital due to suspected acute coronary syndrome had TTS as discharge diagnosis, but this data was probably underestimated [2].

In the Western Countries, TTS affects usually females (female-to-male ratio 9:1) in postmenopausal age (66-80 years of age), while in Japan it's more commonly seen in males due to unknown reasons [3]. Although TTS is not considered a primary cardiomyopathy, a genetic predisposition has been postulated from the description of few familiar cases of TTS [2,4]. TTS is preceded by a stressful event, which probably represents the trigger of acute decompensation in about 71.5% of cases [3]. Particularly, physical (surgical intervention, trauma, cerebral hemorrhage, epileptic seizures, acute exacerbation of asthma or chronic obstructive pulmonary disease, sepsis, cocaine abuse) and emotional (relative's death, receiving tragic news, accidental, financial loss) trigger or both, are described in TTS, accounting respectively for 36%, 27.7% and 7.8% of cases [3]. Thus, a clear precipitating factor is detected in the majority of patients, suggesting the high contribute of environment in TTS.

Moreover, some studies have reported a significant prevalence of anxiety or depression in TTS patients, accounting for 21% of patients and suggesting a correlation between psychiatric disorder and these patients.

PATHOPHYSIOLOGY

The pathophysiology of TTS is complex and actually not completely understood. To date, several etiological mechanisms have been suggested but require experimental confirmation. Catecholamines appear to have a key role in the pathophysiology of TTS: several studies have demonstrated levels of plasma catecholamines (norepinephrine, epinephrine and dobutamine) three or four times greater in patients with TTS compared to those with myocardial infarction [6], suggesting the potential for abnormal release of these hormones following a stressful events. Moreover, patients presenting elevated levels of catecholamines due to abnormal endogenous release (as in pheochromocytoma) or exogenous administration (as in dobutamine stress echocardiography), can frequently develop TTS [7-8]; supporting the hypothesis that catecholamines are involved in the onset of this condition.

On the other hand, the response of cardiovascular system to the stressful event in TTS is peculiar and need to be investigated. Several hypotheses have been proposed but none has been fully clarified.

Some studies had demonstrated that catecholamines are released in different concentration in certain cardiac regions: norepinephrine is mainly released from sympathetic neurons whereas epinephrine is predominantly released from local stores. Moreover, a different sympathetic nerve

terminal density has been showed in myocardial regions, being higher in the cardiac basal than in mid or apical regions. Thus, the heterogeneities of catecholamines' distribution results in a predominant concentration of norepinephrine at the basal level and epinephrine at apical level, with the consequent effect on the expression and function of adrenergic receptors within the myocardial regions [9].

It has been also postulated that apical dysfunction results from the different distribution of β2-adrenoreceptors, which appear to be more prevalent in the apex rather than in the cardiac base [10]. Epinephrine is able to activate these receptors, which in turn couples to inhibitory G-proteins, causing impairment of contractile function, especially in the apical regions [11].

Other hypothesis suggests that TTS is due to a transient vascular insult, as a coronary artery spasm [12] or a spontaneous recanalization of a thrombus in one of the main coronary artery, which can produce a different sudden ventricular dysfunctional pattern on the basis of culprit vessels [13]. These hypothesis are actually refuted because, being cardiac dysfunction typically extended beyond the vascular territory of a single coronary artery, a vascular insult occurring in more than one main coronary artery is very unlikely [14].

On the other hand, the mechanical overload involving limited region of the heart has important implications in TTS. Indeed, it has been postulated that high wall stress causes an increase of energy demand by myocardiocytes, which become "metabolically" insufficient to supply the high demand. Thus, a down-regulation of contractile ability is established in order to preserve vital cell function, resulting in metabolism-perfusion mismatch which can resemble a form of protective stunning of the heart [14,15]. Accordingly, it has been demonstrated that the different contractile pattern of TTS is the result of the heterogeneity of wall stress distribution on the different myocardial regions. To support this hypothesis, it has been pointed out that some cases of TTS show a dynamic left ventricular tract obstruction which can significantly increase the wall stress toward the apical regions [14-16]. Nevertheless, whatever the etiology, there is no doubt that coronary microcirculation plays a key-role in the pathogenesis of TTS [17]. We have clearly demonstrated that a prolonged and reversible coronary microvascular dysfunction within the dysfunctional myocardial segments is the common pathophysiological mechanism of TTS [17].

Myocardial contrast echocardiography, a non-invasive diagnostic tool able to assess myocardial perfusion by using an ultrasound contrast agent as intravascular tracers, provides a conceivable delineation of microvascular patency and intensity. In the acute phase of TTS myocardial contrast echocardiography shows the completely absence of opacification, which indicates a transmural microvascular obstruction, within dysfunctional segments. Interestingly, this microvascular obstruction resolves after adenosine challenge and it is associated with recovery of regional left ventricular myocardial function, thus confirming that microvascular obstruction is sustained by vasoconstriction that, in turn, is responsible of reversible regional myocardial dysfunction [17].

CLINICAL PRESENTATION AND DIAGNOSTIC CRITERIA

Clinical presentation of TTS is generally sudden and mimics of an acute coronary syndrome in regarding of symptoms and signs. Indeed, the most common symptom is chest pain, which occurs at rest and is usually described as a sensation of tightness or pressure, radiating to the shoulder, arm or back and lasting for more than a few minutes. Moreover, approximately half of the patients have shortness of breath (or dyspnea) which reflects the inability of the heart to fill and empty, producing elevated pressures in the blood vessels around the lung. It has usually an abrupt onset at rest and can present a rapid worsening over time, becoming a life-threatening clinical condition. Others symptoms include loss of consciousness (or syncope) or out-of-hospital cardiac arrest but they are less frequently reported. Furthermore, a small proportion of patients, generally hospitalized for non-cardiac diseases, are asymptomatic and identified due to detection of increased levels of cardiac biomarkers or electrocardiographic and echocardiographic abnormalities [figure 2].
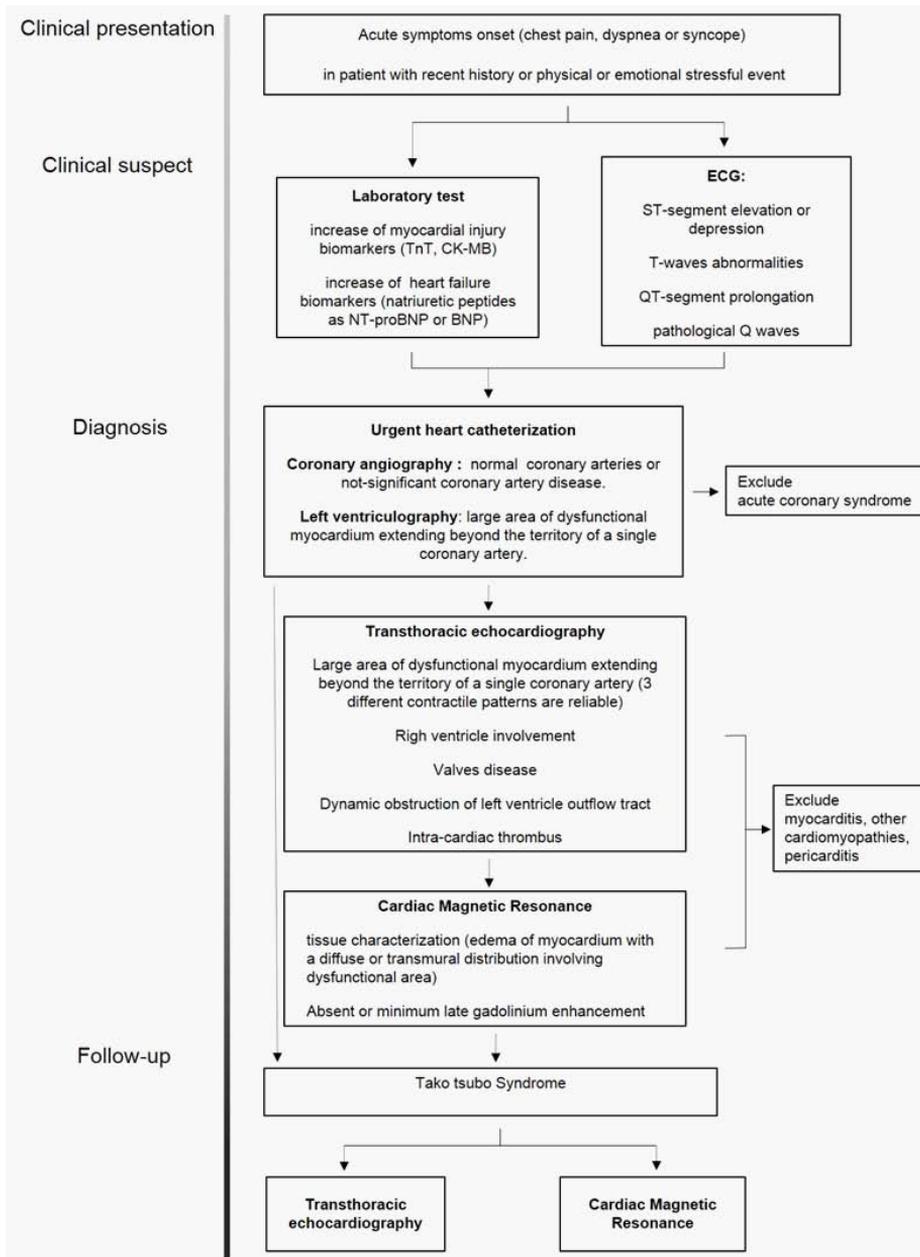
Figure 2: The diagnostic flow-chart of patient with Tako Tsubo Cardiomyopathy **(TTS)**. Clinical presentation of TTS mimics an acute coronary syndrome. Blood samples and Electrocardiogram **(ECG)** performed at first medical contact are not useful to perform differential diagnosis. Thus, patients undergo coronary angiography that typically shows the absence of coronary artery disease and excludes acute coronary occlusion, plaque rupture, coronary dissection, intra-coronary thrombus. At the same time, ventriculography is diagnostic for TTS thanks to its ability to assess left ventricular dysfunction with a characteristic contractile pattern, described in the text.

If the diagnosis is still unclear, trans-thoracic echocardiography and cardiac magnetic resonance will be able to non-invasively evaluate left ventricle morphology and function, identify contractile dysfunction patterns and detect complications. Additionally, cardiac magnetic resonance provides information about tissue characterization. Thus, both diagnostic tools are important in the differential diagnosis and in the follow-up management of these patients in order to non-invasively detect the recovery of ventricular function.

Usually physical examination of patients with TTS does not reveal specific signs, but it can be helpful to assess the hemodynamic status and perform differential diagnosis. The general appearance of patients may vary according to the experienced symptoms; patients may be comfortable or may appear anxious and diaphoretic and in severe distress with an increased respiratory and heart rate. A cool and pale skin is common and points to vasoconstriction.

Hypotension is less frequent and it can suggest a severe left ventricular dysfunction or can be related to a status of cardiogenic shock.

Pulmonary examination is generally normal or can reveal murmurs and rales, if the acute heart failure ensues. Similarly, cardiac examination can detect signs of heart failure, such as a third and fourth heart sound, systolic murmurs and paradoxical splitting of the second heart sound. Additionally, signs of elevated venous pressure, as swelling of the legs, distended jugular veins and hepatojugular reflux, may be found on inspection.

Blood samples generally show high values of cardiac biomarkers denoting myocardial injury (as Troponin or Creatine Kinase MB-fraction) and acute heart decompensation (as Natriuretic Peptide). Although these laboratory abnormalities are detected also in patients with acute coronary syndrome, some authors have pointed out that patients with TTS have lower levels of Troponin and higher levels of B-type Natriuretic Peptide as compared with patients acute coronary syndrome [18].

The basal 12-leads ElectroCardioGram **(ECG)** is the first diagnostic tool performed to symptoms onset, as recommended by current European and American guidelines on acute coronary syndrome [19,20]. Approximately half of patients shows ST-segment elevation that involves precordial leads, or rarely inferior leads, but it is usually transient tending to flatten and normalize over time. The remaining proportion of patients has ST-segment depression or a normal ST-segment. Since these findings are similar between TTS and myocardial infarction, ECG evaluation is not helpful to perform the differential diagnosis. Widespread deep T-waves inversion is often seen at admission or over the first 2-3 days of acute event. Moreover, the prolongation of QT corrected interval occurs frequently, but it usually does not trigger ventricular arrhythmia. Transient pathological Q-waves are rarely detected. A small proportion of patients presents with a new or preexisting Left Bundle Branch Block **(LBBB)** or, less commonly, Right Bundle Branch Block **(RBBB)** [21]. Moreover, some cases of Atrioventricular Block have been occasionally described [22].

Transthoracic echocardiography with color and tissue Doppler is helpful in the acute phase of TTS because it is able to assess left ventricle morphology and function and to detect potential

complications. Typically, echocardiography shows moderate to severe left ventricular dysfunction due to regional wall motion abnormalities extending beyond the myocardial territory of a single epicardial coronary artery [figure 3] [23].
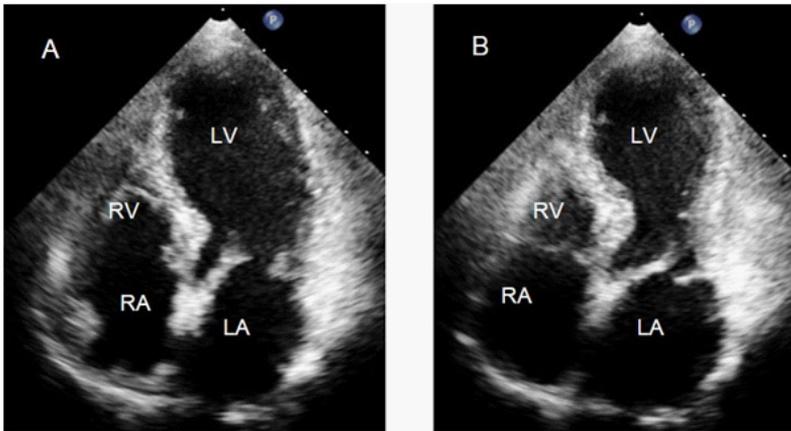

Figure 3: Apical ballooning Tako Tsubo. Trans-thoracic echocardiography allows to assess the typical left ventricular contractile pattern showing, during systole (panel B), the akinesis or hypokinesis of mid and apical segments with the normal or visual hyperkinesis of basal segments. Panel A: diastole. Panel B: systole. LA: left atrium. RA: right atrium. LV: left ventricle. RV: right ventricle.

Echocardiography allows to describe three different contraction patterns of left ventricle [2,3]:

- apical ballooning: the most frequent variant of TTS (accounting for 84% of cases) characterized by akinesia or hypokinesia of mid and apical segments of left ventricle, with normal or enhanced contractility of the remaining myocardial walls [see videos 1,2,3].

Video 1:

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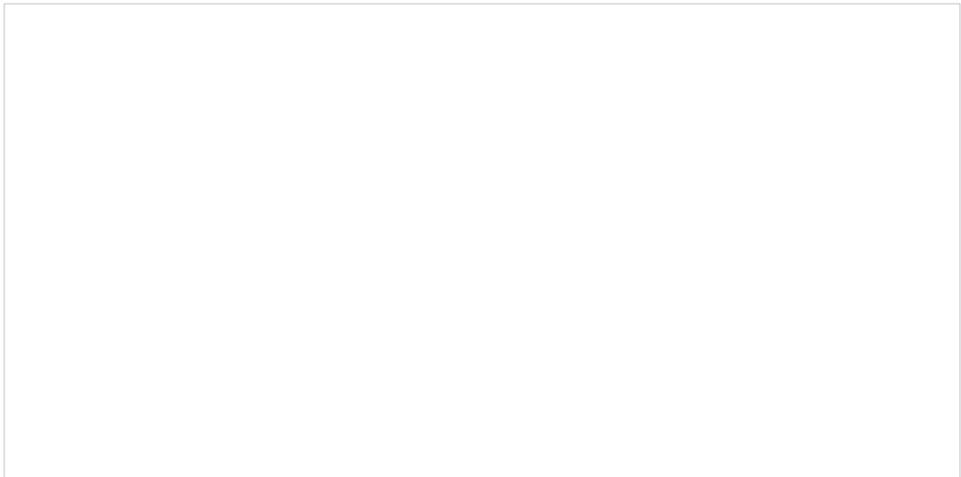
Video 2:

Video 3:

- mid-ventricular ballooning or "apical sparing": defined as akinesia of mid segments of left ventricle sparing the apex.

- basal ballooning, also known as "reverse tako tsubo": defined as akinesia of basal segments and normal contractility of mid and apical left ventricular segments.

Echocardiography is also helpful to evaluate right ventricular involvement, which is present in one third of patients, and to assess valvular disease, as mitral or tricuspid regurgitation, which is often detected in the acute phase of TTS causing by different pathogenetic mechanisms [2,24,25]. Moreover, echocardiography is able to detect intra-cardiac thrombus, which can appear in the context of dysfunctional myocardium [26].

If completed with the intravenous administration of an ultrasound contrast agent, echocardiography can be widely used to assess the wide microvascular perfusion defect that involves the dysfunctional myocardial walls of left ventricle in the acute phase of disease [27] [figure 4].
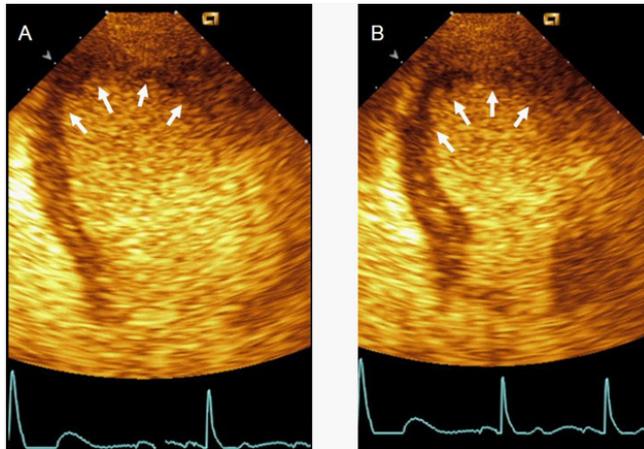

Figure 4: Myocardial Contrast Echocardiography in Apical ballooning Tako Tsubo Syndrome **(TTS)**. Intravenous administration of intravascular contrast agent during trans-thoracic echocardiography shows the lack of opacification in the apical myocardial regions (arrows) during diastole (panel A). Microvascular perfusion defect involves the myocardial dysfunctional areas identified in systolic phase (panel B).

However, although echocardiography is very helpful in the setting of TTS, the diagnosis requires cardiac catheterization in order to evaluate epicardial coronary arteries and rule out the presence of pathological conditions, which can explain the acute clinical presentation, such as significant coronary stenoses, acute plaque rupture, thrombus formation or coronary dissection [2]. Indeed, in the setting of TTS coronary angiography typically reveals normal or near-normal (luminal stenosis <50%) coronary arteries [see videos 4,5]. However, given the older age of patients, significant coronary artery stenosis can be present, but it usually not sufficient to explain the wide myocardial involvement. On the other hand, left ventriculography, performed in the context of cardiac catheterization, is able to identify left ventricular dysfunction and contractile patterns [figure 5] allowing the diagnosis of TTS, as shown in video 6.
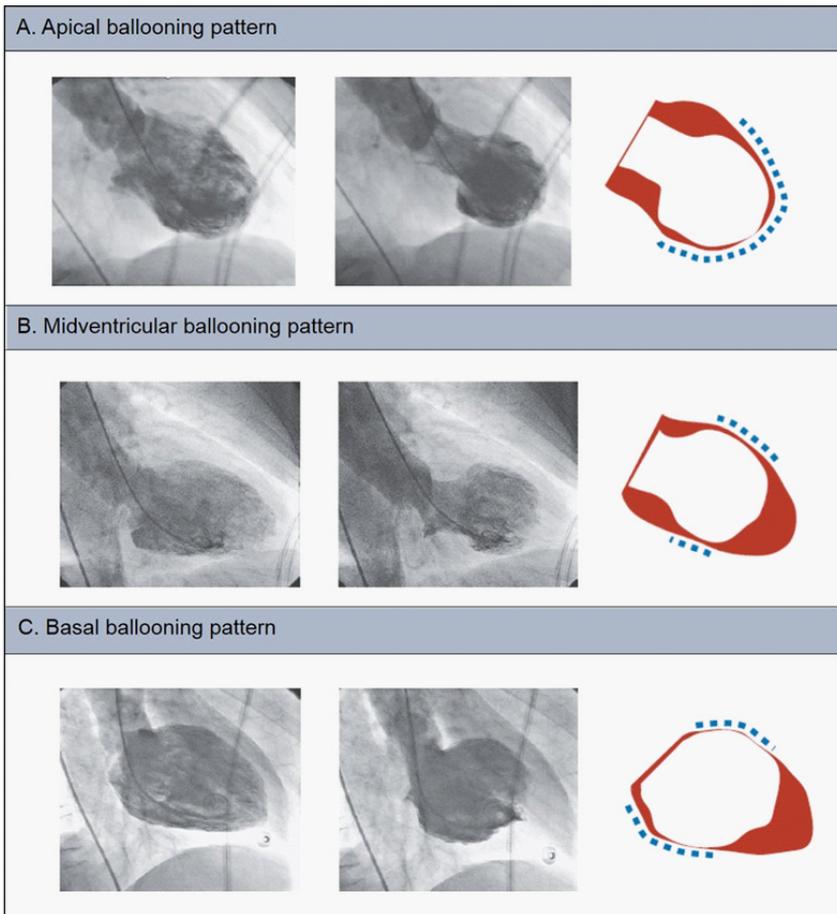
Figure 5: Different left ventricle contractile patterns in Tako Tsubo Cardiomyopathy **(TTS)**. Left ventriculography is able to perform real-time evaluation of diastolic (first column) and systolic (second column) movement assessing the left ventricle dysfunctional contractile pattern of TTS. The third column shows the distribution of left ventricle wall abnormalities in each TTS pattern: red line indicates diastole, white line the systole, while the blue dashed line the localization of contractile myocardial abnormalities. Images modified from Templin C. et al, N Engl J Med. 2015 [3].

Nowadays, the most worldwide accepted criteria to diagnose TTS are proposed by Mayo Clinic in 2004 and revised in the recent years [table 1]. All criteria should be present in order to perform diagnosis [28,29].
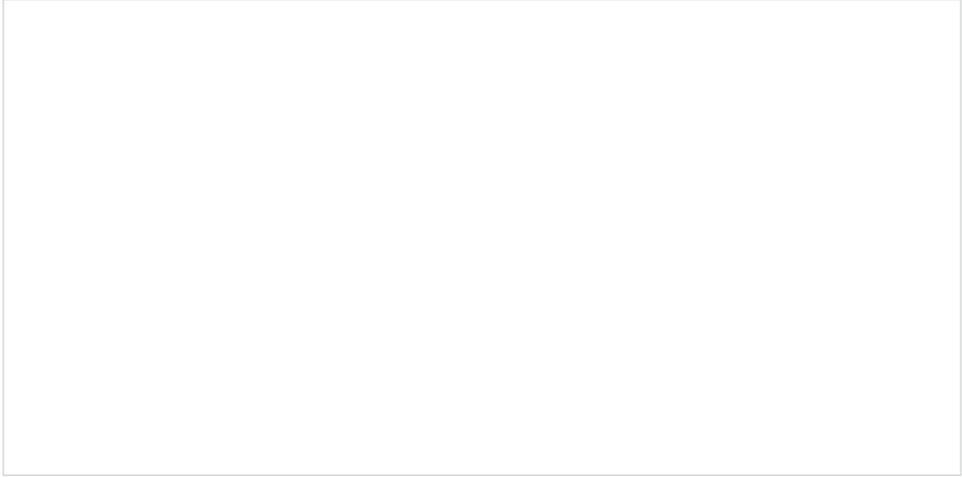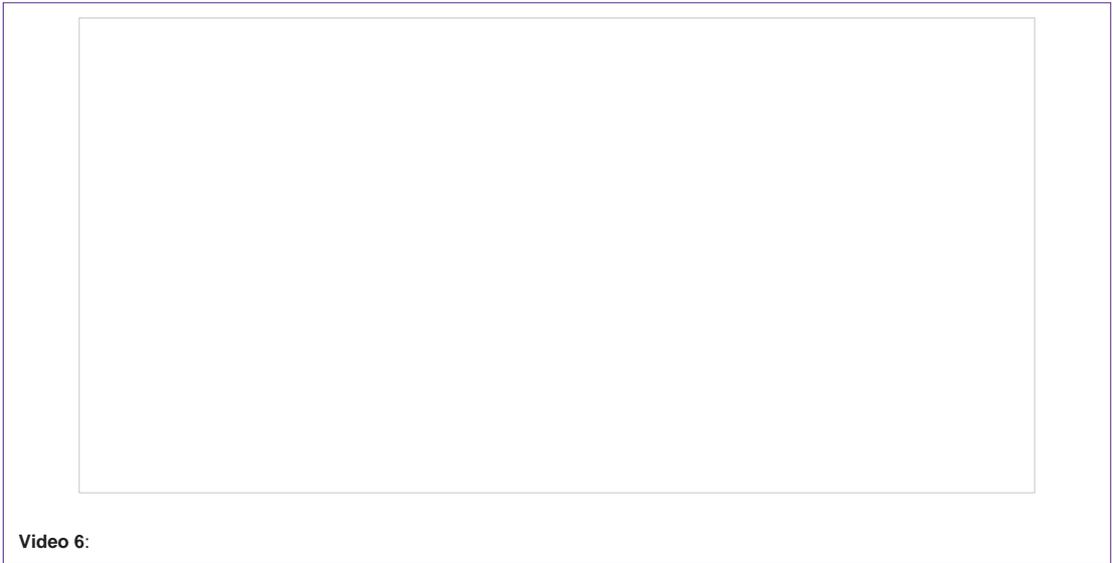
Video 4:
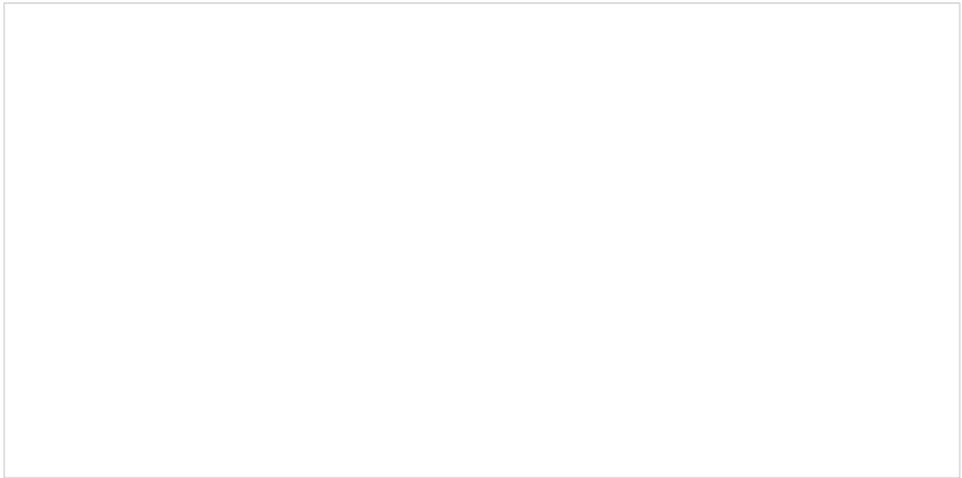
Video 5:

Video 6:

Table 1: Mayo Clinic diagnostic criteria.

1. Transient hypokinesis, akinesis, or dyskinesis of the left ventricular mid segments with or without apical involvement; the regional wall motion abnormalities extend beyond a single epicardial vascular distribution; a stressful trigger is often, but non always, present.
2. Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture.
3. New electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin.
4. Absence of: pheochromocytoma, myocarditis[*].

[*]There is no consensus regarding the nature of cardiac dysfunction detected in patients with Pheochromocytoma.

Table modified from *Madhavan M et al, Herz 2010* [*18*]

In the recent years cardiac magnetic resonance has been increasingly used in the workflow of TTS diagnosis thanks to its ability to perform tissue characterization in addition to assess heart morphology and function. During the acute phase of TTS, cardiac magnetic resonance shows myocardial tissue injury through the presence of edema with a diffuse or transmural distribution in the dysfunctional myocardial wall. These features allow distinguishing TTS from myocarditis and myocardial infarction. Moreover, a normal wash-in and wash-out of gadolinium in myocardial extracellular matrix is usually present in TTS resulting in the almost total lack of "late gadolinium enhancement", which is conversely detectable in myocardial infarction [2,30].

Besides these diagnostic tools, other non-invasive imaging techniques are described in the setting of TTS, as coronary computed tomography and radionuclide imaging, but they have been actually used only in a research context [2].

COMPLICATIONS AND PROGNOSIS

In the setting of TTS, myocardial dysfunction is typically reversible evolving in a total recovery of cardiac function within 12 weeks after the acute event. The improvement of myocardial function over time is easily monitored by trans-thoracic echocardiography and cardiac magnetic resonance, which are both recommended in follow-up of these patients [2].

For these reasons, TTS has been considered as a relatively benign disease with a good prognosis. However, several studies have recently showed a significant incidence of serious complication occurring in both the short and long term [2,3,31].

In the acute phase of disease a systolic heart failure occurred in 12-45% of cases and it may be worsened by a dynamic obstruction of left ventricle outflow tract or acute mitral regurgitation. Moreover, cardiogenic shock has been reported in about 4-20% of patients and has a high rate of in-hospital mortality (17-30%). Arrhythmias are frequent in patients with TTS accounting in 5-15% of cases. Atrial fibrillation is common, while ventricular arrhythmias occur in 3-9% of patients and are limited to the acute phase of disease. Cardiac arrest related to arrhythmic burden is rare (approximately about 4-6% of cases). Asystolia and atrioventricular block have also been described, but infrequently.

Thrombus can be detected within 2-5 days after symptom onset (2-8% of cases) and it's located in the apex of left ventricle. Furthermore, intracardiac thrombus can result in stroke or arterial embolism.

In the acute phase of TTS the mortality rate is 2-5% and it is mainly caused by cardiogenic shock, life-threatening ventricular arrhythmia or mechanical complications, as left ventricular wall rupture or inter-ventricular septal perforation.

In-hospital mortality risk is higher in elderly men presenting signs and symptoms of acute heart decompensation and hemodynamic instability [2,3]. Up to now, different scores had been designed in order to assess mortality risk stratification but they need to be validated in prospective studies [2].

Although the mortality rate is considered higher in the first year after the disease, long-term data are controversial. Some studies show a similar survival-rate between patient with TTS and general population [32]. Conversely, it has been also reported an excess mortality rate in the first 4 years after the acute event but it is surprisingly related to non-cardiac diseases, such as malignancies [33]. Recently, a large retrospective study shows a rate of death from any causes of 5.6% per patient-years and a rate of cardiac and cerebrovascular events of 9,9% per patient-year, with a low incidence of myocardial infarction [3].

After the acute event, a small proportion of patients experience a recurrence of TTS. The 5-year recurrence rate is about 5-22% but it's probably underestimated by the lack of long-term data [2]. Moreover, TTS recurs frequently within the first 4 months after the acute event, even presenting

different left ventricle contraction pattern. It has been also demonstrated that recurrence of TTS does not increase mortality risk of patient, but more data are required to confirm it [2,3].

THERAPEUTIC MANAGEMENT

The management of TTS is empirical due to the lack of randomized clinical trials that have identified the best treatment. Since the recovery of normal myocardial function comes spontaneously over time, the major treatment in the acute phase of TTS is focused on support life, relieve symptoms and minimize complications.

Since no mortality risk score has been actually validated, the best management of this patient comes from clinical judgement and opinion of experts, as the Task Force on Tako Tsubo of European Society of Cardiology [2].

Recently, they have proposed a risk stratification score based on the age of patient, hemodynamic status and clinical presentation, laboratory data, ECG findings (QT segment prolongation, pathological Q waves, ST-segment elevation), echocardiographic findings (grade of left ventricular dysfunction, mitral regurgitation, dynamic obstruction to left ventricle outflow, right ventricle involvement, apical thrombus, septal defect, wall rupture). High risk patients are defined by the presence of at least one major and two minor risk factors, as reported in table 2.

Table 2: Heart Failure Association risk stratification in Tako Tsubo Cardiomyopathy.

Major risk factors		
	Higher risk	**Lower risk**
Age	≥ 75 years	See minor risk factors
Systolic blood pressure	< 110 mmHg	≥ 110 mmHg
Clinical pulmonary edema	Present	Absent
Unexplained syncope, ventricular tachycardia or ventricular fibrillation	Present	Absent
Left ventricle ejection fraction	< 35%	See minor risk factors
Left ventricular outflow tract obstruction	≥ 40 mmHg	Absent
Mitral regurgitation*	Present	Absent
Apical thrombus	Present	Absent
New ventricular septal defect or contained left ventricle wall rupture	Present	Absent
Minor risk factors		
Age	70-75 years	< 70 years
ECG QTc Pathological Q waves Persistent ST elevation**	 ≥500 ms Present Present	 < 500 ms Absent Absent
Left ventricle ejection fraction	35-45 %	≥ 45%
Physical stressor	Present	Absent
Natriuretic peptides BNP NT-proBNP	 ≥ 600 pg/mL ≥ 2000 pg/mL	 < 600 pg/mL < 2000 pg/mL
Obstructive coronary artery disease	Present	Absent
Biventricular involvement	Present	Absent

*Moderate or severe mitral regurgitation

** ≥ 3 days

Table modified from *Lyon A. R. et al,* Eur J Heart Fail. *2015* [*2]*

All patients should be admitted to coronary care unit, in order to monitor patients for the first 24 hours and promptly detect complications. Beta-blockers have not provided beneficial effects in the acute and also in long-term follow-up [3]. Patients presenting with cardiogenic shock should not be treated by catecholamines that probably exacerbate the acute phase but can have beneficial effect from levosimendan or temporary mechanical heart support (e.g. left ventricle assist device, intra-aortic balloon counterpulsation, extracorporeal membrane oxygenation). Moreover, TTS may be associated with severe thrombotic complications, as intra-cardiac or peripheral thrombus that requires oral anticoagulation in the absence of high risk bleeding.

Patient at low risk with mild ventricular dysfunction and no complications may receive heart failure medication, including Beta-blockers and ACE-inhibitors in order to promote favorable ventricular remodeling.

When patient returns home, regular follow-up is recommended with clinical evaluation and cardiac imaging, such as echocardiography or cardiac magnetic resonance.

CONCLUSIONS

TTS is an emerging clinical condition characterized by a transient ventricular dysfunction, usually triggered by an emotional or physical stressful event. The etiology is unknown, reversible microvascular spasm has been described as common pathophysiological mechanism.

Clinical diagnosis of TTS can result difficult due to its similarities with acute coronary syndrome in terms of clinical presentation and instrumental findings and it requires coronary angiographic evaluation to exclude significant coronary artery diseases which can explain the large myocardial dysfunction. Moreover, trans-thoracic echocardiography and cardiac magnetic resonance may be remarkable to non-invasive diagnostic work-up and regular follow-up of TTS patients.

Although the prognosis of these patients has been considered favorable until today, it has been recently revealed that TTS can be associated with serious complications that require prompt identification and treatment.

Nevertheless, no large randomized studies have been performed in order to define the best clinical management of these patients. Thus, many advances still to be made.

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