Ξ. Α. Αποστολίδου
Β’ Καρδιολογική Κλινική Α.Π.Θ.

« Takotsubo Syndrome »

Μάρτιος 2019
«Connecting the pieces of "Takotsubo 'broken heart'"

current state of knowledge

Καμιά σύγκρουση συμφερόντων

Ξ. Α. Αποστολίδου

Β' Καρδιολογική Κλινική ΑΠΘ.

Μάρτιος 2019
• about 90% of TTS patients are women with a mean age of 67–70 years
• around 80% are older than 50 years
• women older than 55 years have a 5-fold greater risk of developing TTS than women younger than 55 years and a 10-fold greater risk than men

It is usually precipitated by acute emotional and/or physical stress
**Emotional triggers**
- depression
- illness of a close person
- suicide attempt
- divorce
- posttraumatic stress disorder
- debt
- huge loss of money
- bankruptcy
- new job
- job loss
- retirement
- bulging at work
- flooding
- earthquake
- storm
- aircraft noise
- argument with the partner / family
- argument with the landlord
- car accident without injury
- downfall without fracture
- influenza
- sepsis
- peritonitis
- wound infection
- death of a family member
- death of partner
- euthanasia of the pet
- fear of speech
- robbery / burglary
- fear of surgery / hospitalization
- move to another city
- fracture
- Happy heart syndrome
  - winning a jackpot
  - birthday party
  - birth of grandchild
  - wedding
  - visiting the opera
  - positive job interview
- operation
- anesthesia
- administration of catecholamines

**Physical triggers**
- cerebral bleeding
- stroke, TIA
- epilepsy, seizure
- migraine
- PRES
- concussion
- aneurysm rupture
- exacerbation COPD
- asthma attack
- pneumonia
- bronchitis
- pulmonary embolism
- giving birth
- vaginal bleeding
- gastrointestinal bleeding
- Crohn's disease
- exacerbation
- hernia incarceration
- cancer
- chemotherapy
- pheochromocytoma
- urosepsis
- urolithiasis
The wall motion abnormalities do not conform to the distribution of a single coronary artery

Echo diagnosis is usually based on **circumferential pattern** of wall motion abnormalities

The wall motion abnormalities do not conform to the **distribution** of a single coronary artery

(1) the presence of acute LV wall dysfunction,
Four Types of Takotsubo Cardiomyopathy.
(2) the absence of significant obstructive coronary artery disease
(3) the rapid improvement of LV systolic function within a few days or weeks during the acute phase two weeks after the event
by Karima Addetia, MD and Roberto M. Lang, MD
Takotsubo cardiomyopathy, a two-stage recovery of left ventricular systolic and diastolic function as determined by cardiac magnetic resonance imaging

Figure 2  LV systolic and diastolic function at admission, pre-discharge, and 3-month follow-up. LVEF, left ventricular ejection fraction; LVPFR, left ventricular peak filling rate indexed to BSA; broken x-axis pre-discharge to follow-up (3 months). Shown as mean with error bars representing SEM.
Publications on “Takotsubo”

15-30 cases per 100,000 per year
What to call the new disease?
Known by

• Apical ballooning syndrome
• Transient left ventricular apical ballooning
• «Ampulla» cardiomyopathy
• Stress Induced Cardiomyopathy
• Stress cardiomyopathy
• Neurogenic Myocardial Stunning
• «Broken Heart Syndrome»

• Takotsubo Syndrome
• «Happy Heart Syndrome»
Under which cardiac disease spectrum should Takotsubo syndrome be classified?
Takotsubo is not a cardiomyopathy☆

Francesco Pelliccia a, Gianfranco Sinagra b, Perry Elliott c, Guido Parodi a, Cristina Basso e, Paolo G. Camici f,*

Takotsubo Syndrome is an acute heart failure syndrome often triggered by emotional or physical stress, where no treatment currently exists, and exact pathogenic mechanisms are unclear.
Pathophysiologic hypothesis
Catecholamine-mediated myocardial stunning
Multivessel epicardial coronary artery spasm
Coronary microvascular dysfunction
Left ventricular outflow tract obstruction and abnormal left ventricular arterial coupling
Acute atherosclerotic plaque rupture in the left anterior descending coronary artery

Predisposing factors
Postmenopausal hormonal status
Thrombophilic status
Genetic polymorphism
Takotsubo syndrome is estimated to represent ~1–3% of all and 5–6% of female patients presenting with suspected STEMI.
Clinical History, ECG, echocardiography and cardiac biomarkers

Coronary angiography

LV angiography

Normal or regional wall motion abnormalities with "epicardial pattern"

Epicardial causes
- Coronary artery plaque
- Coronary dissection

Normal or regional wall motion abnormalities with "microvascular pattern"

Microvascular causes
- Takotsubo syndrome
- Myocarditis
- CMS
- CAS
- Coronary embolism
Epicardial coronary arteries

Atherosclerotic disease
- Stable plaque
  - Reduction in CFR
    - Demand ischaemia ± angina
- Vulnerable plaque
  - Plaque rupture
    - Thrombosis
      - Acute coronary syndromes/infarction

Vasospastic disease
- Focal/transient vasospasm
  - Prinzmetal angina
- Persistent vasospasm
  - Myocardial infarction

Coronary microcirculation

Microvascular dysfunction
- Impairs coronary physiology and myocardial blood flow in subjects with risk factors
- Contributes to myocardial ischaemia in CAD and CMP
- Induces severe acute ischaemia ‘Takotsubo’

These three mechanisms can overlap
Spontaneous multi-vessel epicardial coronary spasm is not a consistent finding in patients with TS and has been reported in only 2% of patients with TS.

Multi-vessel coronary vasospasm could be induced after acetylcholine administration in only 21% of patients with TS in one study and in 24 (28.6%) of 84 patients in another study.
A combined perfusion/metabolism positron emission tomography/CT (PET/CT) study was conducted on the seventh post-interventional day and 3 months later.
Figure 1  Myocardial contrast echocardiography. (A) A clear perfusion defect is present at baseline within LV apical...
The coronary Flow Reserve is transiently impaired in TTS

Meimun et al, JASE 10.1016/j.echo.2007.05.024
In normal human hearts, the density of sympathetic nerve endings is approximately 40% higher in the basal myocardium than in the apical myocardium. 

**Apex**

is the anatomical structure without a three-layered myocardial structure (as in the basal and mid-cavity segments); an easy loss of LV apex elasticity after excessive expansion.

**stimulus trafficking**

- Epinephrine–$\beta_2$AR–$G_i$ signaling
- Negatively inotropic
hypercontractility of basal segments.

110 mmHg pressure gradient

next day

Valsalva manoeuvre.
a new study shows that this syndrome is characterized by macrophage infiltration in the myocardium, changes in circulating monocyte subsets and increased levels of pro-inflammatory cytokines in the blood, with some of these changes persisting for ≥5 months.
The initial clinical presentation mimics acute coronary syndrome, with the leading symptoms of chest pain and dyspnea. Likewise, electrocardiography (ECG) and laboratory findings do not allow for the reliable discrimination of these entities. Therefore, the final diagnosis is based on several criteria and requires a multimodality imaging approach.
the final diagnosis is based on several criteria and requires a multimodality imaging approach.
International Expert Consensus Document on TTS


doi:10.1093/eurheartj/ehy076

International Expert Consensus Document on Takotsubo Syndrome (Part II): Diagnostic Workup, Outcome, and Management

doi:10.1093/eurheartj/ehy077
1. Patients show transient left ventricular dysfunction (hypokinesia, akinesia, or dyskinesia) presenting as apical ballooning or midventricular, basal, or focal wall motion abnormalities. Right ventricular involvement can be present. Besides these regional wall motion patterns, transitions between all types can exist. The regional wall motion abnormality usually extends beyond a single epicardial vascular distribution; however, rare cases can exist where the regional wall motion abnormality is present in the subtended myocardial territory of a single coronary artery (focal TTS).

2. An emotional, physical, or combined trigger can precede the takotsubo syndrome event, but this is not obligatory.

3. Neurologic disorders (e.g. subarachnoid haemorrhage, stroke/transient ischaemic attack, or seizures) as well as pheochromocytoma may serve as triggers for takotsubo syndrome.

4. New ECG abnormalities are present (ST-segment elevation, ST-segment depression, T-wave inversion, and QTc prolongation); however, rare cases exist without any ECG changes.

5. Levels of cardiac biomarkers (troponin and creatine kinase) are moderately elevated in most cases; significant elevation of brain natriuretic peptide is common.

6. Significant coronary artery disease is not a contradiction in takotsubo syndrome.

7. Patients have no evidence of infectious myocarditis.

8. Postmenopausal women are predominantly affected.

There is a lack of a worldwide consensus diverse definitions
Coronary Angiography & Left Ventriculography

InterTAK Diagnostic Score
- Female sex: 25 points
- Emotional stress: 24 points
- Physical stress: 13 points
- No ST-segment depression*: 12 points
- Psychiatric disorders: 11 points
- Neurologic disorders: 9 points
- QTc prolongation: 6 points

≤ 70 points: Low/intermediate probability of TTS
> 70 points: High probability of TTS

Red flags of acute infectious myocarditis:
- Signs and/or symptoms of viral infections
- Elevated ESR and/or CRP
- Pericardial effusion

ACD

CCTA

CMR

ACS

Acute infectious myocarditis
Figure 2 (A) Diffuse, patchy late enhancement distributed over the septal and lateral wall as indicated by arrows ...
Focal LV ballooning

Four months later
Symptoms and signs

• Acute chest pain ± palpitations
• Dyspnea,
• Syncope,
• incidentally by new ECG changes, or
• by a sudden elevation of cardiac biomarkers
• manifestation of the underlying acute illness when induced by Physical Stress (ischaemic stroke or seizure-triggered etc.)
• Or with symptoms arising from its complications
• Heart Failure
• Pulmonary oedema
• Stroke
• Cardiogenic Shock
• Cardiac Arrest

“acute, reversible, heart failure syndrome”
Predictors of in-hospital mortality include hemodynamic instability (cardiogenic shock, use of catecholamine drugs), age >70 years, physical illness trigger, male gender, and cardiac arrest.
Autopsy shows a wide penetrating apical rupture in a patient with takotsubo cardiomyopathy.
Complications of Takotsubo Syndrome

- Acute heart failure
- Pulmonary edema
- Cardiogenic shock
- Cardiac arrest
- Life-threatening arrhythmias
- Left ventricular outlet tract obstruction
- Mitral regurgitation
- Cardiac rupture
- Thrombo-embolism
- Death
In-hospital Complications

- **Frequent**
  - Acute heart failure (12-45%)
  - LVOTO (10-25%)
  - Mitral regurgitation (14-25%)
  - Cardiogenic shock (6-20%)

- **Moderate**
  - Atrial fibrillation (5-15%)
  - LV-thrombus (2-8%)
  - Cardiac arrest (4-6%)
  - AV-block ~5%

- **Rare**
  - Tachyarrhythmia (2-5%)
  - Bradyarrhythmia (2-5%)
  - Torsades-de-pointes (2-5%)
  - Death (1-4.5%)
  - Ventricular tachycardia/fibrillation ~3%
  - Acute ventricular septal defect <1%
Mild TTS w/o signs of HF*
Cardiology unit with telemetry monitoring for at least 48 hrs
Consider:
- ACE inhibitor or ARB
- Beta-blocker

*Avoid:
- Inotropes as:
  - Adrenaline
  - Noradrenaline
  - Dobutamine
  - Milrinone
  - Isoproterenol

Hypotension/Cardiogenic Shock*
Intensive Care Unit (preferentially)

Heart Failure/Pulmonary Edema*
Intermediate Care Unit (preferentially)
Consider:
- ACE inhibitor or ARB
- Beta-blocker
- Diuretics (if no LVOTO)
- Nitroglycerin (if no LVOTO)

LVOTO
Consider:
- IV fluid (if no HF)
- Short acting Beta-blocker
- LVAD (Impella)

Avoid:
- Diuretics
- Nitroglycerin

Primary pump failure
Consider:
- Levosimendan
- LVAD (Impella)
- VA-ECMO
a Defibrillator monitor showing polymorphic VT and b 12 lead ECG showing sinus rhythm with markedly prolonged QTc
narrow complex tachycardia (likely fascicular VT), and b Defibrillator monitor showing lack of response to DC cardioversion
continuous ECG monitoring at coronary care units for at least 48 hours in all patients with suspected TTS

- Ventricular arrhythmias: n = 23 (57.5%)
  - Ventricular fibrillation: n = 8 (20.0%)
  - Asystole: n = 5 (12.5%)
  - Pulsless electrical activity: n = 3 (7.5%)
  - Ventricular tachycardia: n = 16 (40.0%)
  - Complete AV block: n = 7 (17.5%)
  - SA block: n = 1 (2.5%)
Three months or until RWMA recovery

Consider:
- ACE inhibitor or ARB

Treatment of other underlying disorders, e.g.

Coronary artery disease:
- Aspirin
- Statin

Depression/Anxiety:
- Combined psycho-cardial rehabilitation

Recurrence Prevention

Consider:
- Hormone replacement
- ACE inhibitor or ARB
Secondary forms of Takotsubo cardiomyopathy: A whole different prognosis

Núñez-Gil et al.

discharge, a more frequent prescription of beta-blockers and statins in primary-TKS patients was seen. Secondary forms displayed more in-hospital stay and evolutive complications: death (hazard ratio (HR): 3.41; 95% confidence interval (CI): 1.14–10.16, \( p=0.02 \)), combined event variable (MACE) (HR: 1.61; 95% CI: 1.01–2.6, \( p=0.04 \)) and recurrences (HR: 1.85; 95% CI: 1.06–3.22, \( p=0.02 \)).

**Conclusion:** Secondary TKS could present or mark worse short and long-term prognoses in terms of mortality, recurrences and readmissions. We propose a simple working nomenclature for TKS.

**Keywords**
Takotsubo syndrome, RETAKO, secondary, classification, nomenclature, prognosis
LV thrombus was defined as an echo-dense mass, contiguous but distinct from the endocardium, located in an area of a-/hypokinesis that was seen in both systole and diastole in at least 2 echocardiographic views.
RV thrombus has also been reported in cases of biventricular TS with or without pulmonary embolic event.

The thrombus is mural in about 40% and protruding in about 60%.

**left ventricular thrombus (LVT)**

Thrombo-embolism has been reported in 2% to 14% of patients with TS in general.

The most common reported sites of cardio-embolic complications are cerebral, renal, and peripheral limb arteries.

LVT has been reported in 1% to 8%.

One-third of patients with LVT in TS develop embolic complications.

Cases of cardio-embolic events in the absence of detectable LVT have also been reported.

<table>
<thead>
<tr>
<th>Authors</th>
<th>No of patients with TS</th>
<th>No of patients with thrombo-embolism (both LVT and cardio-embolism) (%)</th>
<th>No of patients with LVT (%)</th>
<th>No of patients with cardio-embolism (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haghi et al(^{13})</td>
<td>52</td>
<td>4 (8%)</td>
<td>4 (8%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Mitsuma et al(^{14})</td>
<td>21</td>
<td>3 (14%)</td>
<td>1 (4.8%)</td>
<td>2 (9.5%)</td>
</tr>
<tr>
<td>Sharkey et al(^{15})</td>
<td>136</td>
<td>5 (3.7%)</td>
<td>5 (3.7%)</td>
<td>2 (1.5%)</td>
</tr>
<tr>
<td>Kurisu et al(^{11})</td>
<td>95</td>
<td>5 (5.3%)</td>
<td>5 (5.3%)</td>
<td>1 (1.1%)</td>
</tr>
</tbody>
</table>
Oral anticoagulation in high risk Takotsubo syndrome: When should it be considered and when not?
The anticoagulation should be continued for 2 to 3 months or at least until the LVWMA and LVT have resolved. The LVT usually resolves when the LVWMA improves or resolves.
Death during admission occurred in 2.4%, 
annual rate of total mortality was 3.5% (22% cardiac deaths) 
annual rate of recurrence >1% 
in 36% of patients, onset of TTS was preceded by emotional stress 
a physical stressor was identified in 36% 
ST-segment elevation was evident in 44% 
symptoms and/or signs of acute heart failure occurred in approximately one-half of all cases 
malignant ventricular arrhythmias were recorded in 10% 
shock was present in 19% 
Hypertension, dyslipidemia, diabetes mellitus, and smoking were detected in 59%, 34%, 14%, and 23% 
the prevalence of comorbidities: pulmonary [14%], endocrinological [10%], neurological [15%] and psychological diseases [18%], as well as malignancy (17%) 
Older age, physical stressors, and atypical ballooning forms were the most relevant factors associated with an unfavorable long-term prognosis
A 67-year-old German female with a history of hypertension under therapy with Metoprolol 47.5 mg/od, Ramipril 2.5 mg/od, and aspirin (100 mg/od) was admitted to the emergency department with chest pain. On admission, she did not report about an obvious emotional stress situation.

The initial electrocardiogram showed sinus rhythm and T-inversions in the leads I, II, aVL, V1, and V2. The coronary angiography showed a mild coronary artery disease with a 50% stenosis in LAD. Within one week, wall motion abnormalities and ejection fraction fully recovered. Contrast enhanced CMR excluded myocardial necrosis as well as ischemia in the anterior wall.

**On admission she did not report about an obvious emotional stress situation.**

North et al. Cases Journal 2008 1:331
A 67-year-old woman presented with dyspnea and chest pain. She had no history of smoking, diabetes mellitus, hypertension, or obesity and had not a family history of ischemic heart disease. ECG revealed sinus rhythm with ST-elevations in the inferior leads and in V3 through V5 with anterior T-wave inversions. Troponin T = 528 ng/L.

Half an hour after CAG, the patient developed expressive aphasia, right-sided hemiparesis, and paresthesia.
Endovascular thrombectomy

left middle cerebral artery

mTICI score 3
Regional Hypokinesia

No evidence of focal LGE

Apart from the sub-epicardial infarction area in the apical-inferior wall.
Three days prior to admission, the patient had been told that her son had been subjected to robbery and abuse. Minutes after this intense emotional stress, the patient experienced shortness of breath associated with nausea and vomiting.

The dyspnea continued and 3 days later, the patient started to have chest pain, which resulted in admission of the patient.
the possibility of spontaneous coronary artery dissection (SCAD) in LAD cannot be completely excluded. Spontaneous resolution and recanalization of the dissected vessel is also a characteristic feature of SCAD.

During the last few years, many cases with findings of TS and SCAD in the same patient have been reported.

Clinical Cardiology. 2019;42:312–319
acute myocardial infarction due to acute coronary occlusion from a coronary embolus may be a complication of TSS
An 83-year old woman, with no medical history of interest, who consulted for a 12 hour history of central chest pain with no clear triggering factor.
• After 10 days of hospitalization, the patient was discharged with preserved LV systolic function

• At the 3-month follow-up examination, she was in NYHA functional class I, with preserved overall and segmental LV systolic function and persistence of the ECG changes
“Experience is the name we give to our mistakes”

Oscar Wilde