The TakoTsubo spectrum

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Case Report

- M 75 y
- Ischemic heart failure
- GABCx3
- LVEF 25%
- CRTD

- F 72 y
- HTN
- Precordial chest pain
Takotsubo Cardiomyopathy

- Cardiomyopathy characterized by transient apical and midventricular LV dysfunction in the absence of significant coronary artery disease that is triggered by emotional or physical stress.
  - In setting of depressed/abnormal function of distal and apical LV segments there is compensatory hyperkinesis of basal walls → “ballooning” of apex during systole.
- Typically recover normal LV function in 1-4 weeks.
Takotsubo Cardiomyopathy

- 1st described in Japan in 1991
- Named after the tako-tsubo, which is an octopus trap
  - Shape of the trap is similar to the appearance of LV apical ballooning noted in patients with this form of cardiomyopathy
- Was later described elsewhere as well and is being increasingly recognized.
Takotsubo Cardiomyopathy

Aliases

- Takotsubo cardiomyopathy
- Stress-induced cardiomyopathy
- Transient left ventricular apical ballooning syndrome
- Apical ballooning syndrome
- Broken heart syndrome
- Ampulla cardiomyopathy
Happy Heart Syndrome

Positive emotions and Takotsubo syndrome: ‘happy heart’ or ‘Diagoras’ syndrome?
Spyridon Katsanos, Angeliki Filippatou, Frank Ruschitzka, Gerasimos Filippatos

DOI: http://doi.org/secure.sci-hub.io/10.1093/eurheartj/ehw197
Published: 01 June 2016 Article history

Takotsubo syndrome (TTS) has been traditionally related with negative emotion. However, in a recent analysis from the International Takotsubo Registry ‘joyful or socially desirable events’ have also been shown to trigger it: birthday party, wedding, becoming grandmother, grandchildren visiting from abroad, etc. The study did not find any major differences in the clinical presentation of TTS triggered by happy when compared with those trigged by negative life events. Interestingly, TTS after a joyful event was 1.1% among all TTS registered cases and only 4.1% among cases with definite emotional trigger. This finding has been attributed to a possible higher threshold of emotional stimulation needed in case of joyful events. While TTS as a broken heart syndrome has been recognized since 1990, TTS as a happy heart
Epidemiology

- May account for up to 2% of suspected ACS
- In-hospital mortality ranges 0-8%
- Much more common in women (~90%), especially postmenopausal women (>80% of cases)
- Mean age 58-75 years
- Triggers: death of loved one, other catastrophic news, devastating financial losses, natural disasters, physical illness/ICU, etc.
Diagnostic Criteria
Mayo Clinic diagnostic criteria, all four of which are required for the diagnosis

• Transient left ventricular systolic (LV) dysfunction (hypokinesis, akinesis, or dyskinesis). The wall motion abnormalities are typically regional and extend beyond a single epicardial coronary distribution; rare exceptions are the focal (within one coronary distribution) and the global type.

• Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture. If coronary disease is found, the diagnosis of stress cardiomyopathy can still be made if the wall motion abnormalities are not in the distribution of the coronary disease. This exception is made since some patients with stress cardiomyopathy have concurrent coronary disease (15.3 percent in the International Takotsubo registry).

• New electrocardiographic abnormalities (either ST-segment elevation and/or T wave inversion) or modest elevation in cardiac troponin.

• Absence of pheochromocytoma or myocarditis.
# Types

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Images</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Apical Type</td>
<td></td>
<td><img src="image" alt="Image A" /> <img src="image" alt="Image B" /> <img src="image" alt="Image C" /> <img src="image" alt="Image D" /> <img src="image" alt="Image E" /> <img src="image" alt="Image F" /> <img src="image" alt="Image G" /> <img src="image" alt="Image H" /></td>
<td>N=1400 (81.7%) N=255 (14.6%) N=35 (2.2%) N=25 (1.5%)</td>
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History

- Acute emotional stress (25% of cases)
  - Unexpected death in the family
  - Confrontational argument
  - Severe anxiety

- Physical stressor (30% of cases)
  - Asthma attack
  - Exhaustion
  - Sepsis

- Idiopathic (30% of cases)
  - Takotsubo
Symptoms and signs
(International Takotsubo Registry)

-The most common symptoms were chest pain 75.9%, dyspnea 46.9%, and syncope 7.7%.

-Some patients develop symptoms and signs of heart failure, tachyarrhythmias (including ventricular tachycardia and ventricular fibrillation), bradyarrhythmias, sudden cardiac arrest, or significant mitral regurgitation.

-Approximately 10% of patients with stress cardiomyopathy develop symptoms and signs of cardiogenic shock (such as hypotension, abnormal mental status, cold extremities, oliguria, or respiratory distress).

-Left ventricular outflow tract obstruction, induced by left ventricular basal hyperkinesis produces a late peaking systolic murmur, similar to that heard in patients with hypertrophic cardiomyopathy and can contribute to the development of shock and cause severe mitral regurgitation.
ECG

- At presentation:

ST-elevation in pre-cordial leads
• Later that day

Resolution of ST-elevation
Development of T-wave inversion
Angiography

- The absence of coronary artery stenosis\(^1\)
- Mid-ventricular wall akinesia/dyskinesia, with hypercontractile basal segments producing the characteristic appearance\(^6\)
- Abnormalities in the apical wall, sparing the base

Fig. Ventriculogram in diastole (A) and systole (B)\(^6\)
Echocardiography

• Acutely reduced ejection fraction

Cardiac enzymes

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Takotsubo</th>
<th>STEMI</th>
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<tbody>
<tr>
<td>Initial TnI</td>
<td>1.1</td>
<td>1.9</td>
</tr>
<tr>
<td>Peak TnI</td>
<td>4.9</td>
<td>7.3</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>33</td>
<td>25</td>
</tr>
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</table>

• TnI rises in Takotsubo
• In Takotsubo the peak TnI rise is disproportionate to the level of LV dysfunction
Pathogenesis

- **Catecholamine excess**
  - Norepinephrine levels are elevated in ~75% in some studies
  - Plasma catecholamines are significantly higher than in cases of MI
  - May induce microvascular spasm or dysfunction → myocardial stunning or direct myocardial toxicity
  - Limited endomyocardial biopsy data c/w histologic signs of catecholamine toxicity

- **Coronary artery spasm or microvascular spasm**

- **Myocarditis**
Estrogens

• Hormones are thought to be the key in explaining the high proportion of cases in PMW
• Estrogen may influence coronary artery vasoreactivity and its absence may increase risk of microspasm
Cardioprotective effects of Estrogen Protection against acute Takotsubo syndrome

No TTS in females

Ovariectomy increased mortality

Estrogen reduced mortality

OVX mortality was both pump death and VF
Spontaneous multivessel vasospasm

- Spontaneous multivessel vasospasm reported
- Provocation-induced vasospasm was present in 34 of 123 patients studied (27.6%)

Pilgrim et al IJC 2008 124: 283-292
Aborted Myocardial Infarction

Takotsubo Cardiomyopathy Is Not Due to Plaque Rupture: An Intravascular Ultrasound Study

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ABSTRACT

Background: Plaque rupture with subsequent transient thrombotic coronary occlusion by a fast-dissolving clot is one of the proposed pathogenic mechanisms in Takotsubo cardiomyopathy (TC).

Hypothesis: The aim of this study was to seek evidence for the hypothesis of transient coronary thrombosis as the underlying mechanism of TC by means of intravascular ultrasound (IVUS).

Methods: In our database of 63 consecutive patients with TC we identified 10 patients (16%) who had undergone IVUS during their initial left heart catheterisation.

Results: A median length of 67 mm of the left anterior descending artery was analyzed (interquartile range [IQR] 63.3–70.1 mm). Median lumen diameter, median vessel diameter, median plaque and media volume were 2.9 mm (IQR: 2.7–3.1 mm), 4.2 mm (IQR: 3.8–4.4 mm), and 90.9 mm³ (IQR: 70.4–101.4 mm³), respectively. Plaque rupture, positive remodeling, and presumed intracoronary thrombus were absent in all patients.

Conclusion: In conclusion, plaque rupture does not account for the regional wall motion abnormalities observed in TC. The previously reported observation of plaque rupture in TC seems to constitute an incidental finding. We suggest that the theory of aborted myocardial infarction as the underlying cause of TC should be abandoned once and for all.

Haghi et al Clinical Cardiology 2010 (May 20) 33 307 - 310
Takotsubo Syndrome

1. Why negative inotropic response?
2. Why full recovery?
3. Why regional effect - apical and mid LV suppression with basal sparing?
Takotsubo Syndrome and the $\beta_2$AR Hypothesis

Stress (Takotsubo) cardiomyopathy—a novel pathophysiological hypothesis to explain catecholamine-induced acute myocardial stunning

Alexander R Lyon*, Paul SC Rees, Sanjay Prasad, Philip A Poole-Wilson and Sian E Harding

2008 5 (Jan) pp1-8
β Adrenergic Receptor Signalling Pathways in Ventricular Cardiomyocytes

- β₁AR
- Gsα
- β2AR
- Gsα
- βγ
- AC
- ATP
- cAMP
- PKA
- PTK
- GRK5
- Decreased rate
- Decreased force
- Prolonged relaxation
- Anti-apoptotic Pathways e.g. p38MAPK, PI3K + Akt
- Increased rate
- Increased force
- Accelerated relaxation
- Arrhythmias
- Cell death (necrosis, apoptosis)
Transgenic Mouse Model Overexpresses Human β2 AR

Negative inotropic effect of high dose adrenaline via human β2 adrenoceptor coupled to Gi protein

Gi protein inhibition by PTX

Heubach et al Molecular Pharmacology 2004 65: 1313-1322
Adrenaline-Induced Negative Inotropism

- High adrenaline concentrations
- Mediated via the $\beta_2$AR switch to the $G_i$ pathway (stimulus trafficking = biased agonism)
- Fully reversible
  - washout during *in vitro* studies
  - $\beta_2$AR dephosphorylation
  - $\beta_2$AR internalisation and degradation
- Several $\beta_2$AR blockers mediate negative inotropism via this mechanism e.g. propranolol
Why Regional Effect

Typical anatomical variant

Apical and mid LV suppression with basal sparing?
Apical-Basal Physiological Gradients

1. Sympathetic Innervation

Fig. 7. TH-positive nerves at the base (A) and the apex (B) in the ventricle. TH-positive nerves (arrows) are distributed more at the base than at the apex.

Fig. 11. Comparison of nerve distribution between the base and apex in the ventricle. Bar graph shows the total number of nerve-positive sections at the base and apex in the ventricle. LV, left ventricle; RV, right ventricle. **P < 0.01
Increased responsiveness of left ventricular apical myocardium to adrenergic stimuli

Hidezo Mori, Shiro Ishikawa, Shoji Kojima, Junichi Hayashi, Yukihiro Watanabe, Julien I E Hoffman, and Haruka Okino
Cardiovascular Research 1993;27:192-198

Table IV Distribution of β adrenergic receptor density (n=5), Values are means (SEM).

<table>
<thead>
<tr>
<th>Segment</th>
<th>B_max (fmol-mg⁻¹ protein)</th>
<th>K_d (nM)</th>
</tr>
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<tbody>
<tr>
<td>Basal segment</td>
<td>341(35)*</td>
<td>2.0(0.6)</td>
</tr>
<tr>
<td>Mid segment</td>
<td>377(32)*</td>
<td>2.3(0.4)</td>
</tr>
<tr>
<td>Apical segment</td>
<td>455(45)</td>
<td>2.3(0.6)</td>
</tr>
</tbody>
</table>

B_max=density of receptors; K_d=dissociation constant.
*p<0.05 v apical segment. two way ANOVA

Fig. 2. Distribution of cardiac β-adrenoceptors. The density of β receptors (fmol/mg protein) is shown for the following areas of the heart: LA= left atria; RA= right atria; LV1= proximal area of distribution of the left anterior descending artery (LAD); LV2= distal area of distribution of the LAD; LV3= posterior aspect of the left ventricle; S= septum and RV= right ventricle.
Takotsubo Syndrome and the $\beta_2$AR Hypothesis

Noradrenaline – $\beta_1$ – Gs signalling
POSITIVELY INOTROPIC
PROAPOPTOTIC

Adrenaline – $\beta_2$ – Gi signalling
NEGATIVELY INOTROPIC
ANTIAPOPTOTIC

= sympathetic nerve

Cardiovascular magnetic resonance (CMR) may be helpful in the diagnosis and evaluation of stress cardiomyopathy, particularly when the echocardiogram is technically suboptimal and/or there is coexistent coronary artery disease.

CMR may assist in the differential diagnosis, delineate the full extent of ventricular abnormalities, and identify associated complications.
Does the heart fully recover following acute Takotsubo syndrome?
Abnormal myocardial oedema persists at 3 months

Whole-slice T2-weighted signal intensity (T2-w SI) data from normal controls (A) and patients with acute Takotsubo syndrome (B).

Christopher Neil et al. Heart 2012;98:1278-1284
Acute Complications

- Tachyarrhythmias, bradyarrhythmias
- Pulmonary edema
- Cardiogenic shock
- Transient LV outflow tract obstruction
- Mitral valve dysfunction
- Acute thrombus formation and stroke
- Death
Management

- Supportive, conservative therapy
  - Hydrate, remove stress (if possible)
- Treat LV dysfunction with standard heart failure regimen- including beta blocker, ACE inhibitor, diuretics (if volume overloaded), aspirin
  - Usually treated for ~6 months
- For pts who are hypotensive with shock, perform echo to evaluate for LVOT obstruction.
  - No LVOT obstruction $\rightarrow$ inotropes, IABP if needed
  - +LVOT obstruction $\rightarrow$ NO inotropes (can worsen obstruction), use beta blockers (+/- $\alpha$ agonist Phenylephrine), IABP if needed
  - +/- fluid resuscitation (evaluate pulmonary status)
Prognosis

Overall, good prognosis. If patient survives the acute phase, long-term prognosis is excellent.

- 0-8% in-hospital mortality, likely closer to 1-2%
- Recovery of LV function, typically in 1-4 weeks
- Late sudden death (rare) and recurrent disease (<10%) have been reported
Inter TAK registry
InterTAK Diagnostic Score

The InterTAK Diagnostic Score predicts the probability of the diagnosis of a Takotsubo cardiomyopathy event and differentiates patients from Acute coronary syndrome. The InterTAK Diagnostic Score is based on data from the International Takotsubo Registry and includes 7 clinical variables that can be easily applied without using invasive imaging tools. The maximal score yields 100 points.

- **Female Sex** (25 points)
- **Emotional Stress** (24 points)
- **Physical Stress** (13 points)
- **No ST-Segment Depression** (12 points)
- **Acute, Former or Chronic Psychiatric Disorder** (11 points)
- **Acute, Former or Chronic Neurological Disorder** (9 points)
- **Prolonged QTc Time** (Female > 460ms; Male > 440ms) (6 points)

**Total InterTAK Diagnostic Score:** 49

**Probability of Takotsubo:** 15.4%
DO NOT TAUNT THE OCTOPUS