**Takotsubo Cardiomyopathy**

Also Known As:
- Transient Left Ventricular Apical Ballooning Syndrome
- Stress Cardiomyopathy
- Ampulla-Shaped Cardiomyopathy
- Neurohumoral Myocardial Stunning
- Catecholamine Induced Cardiomyopathy
- Neurocardiogenic Injury
- Broken Heart Syndrome

“Takotsubo Stress Cardiomyopathy” (TSCM)
Demographics of TSCM

Age: ~ 97% > 50 years
Sex: ~ 90% females
Race: All racial/ethnic groups
More frequent in summer months

Clinical Presentation of TSCM
Mimics acute anterior myocardial infarction
Chest pain
Shortness of breath
Anterolateral ECG abnormalities
Elevated markers of myocardial injury
Ventricular arrhythmias
Hemodynamics vary from normal to cardiogenic shock
Often onset in emotionally stressful situations

Mayo Criteria for Diagnosis of TSCM
(Transient Left Ventricular Apical Ballooning Syndrome)

All Four Required:
1. Transient left ventricular apical and/or mid-ventricular wall-motion abnormalities, beyond a single artery distribution
2. Absence of significant coronary disease
3. New ECG abnormalities (either ST-segment elevation or T-wave inversion) or troponin-I elevation
4. Absence of:
   Pheochromocytoma
   Myocarditis
   (Removed: Acute head trauma and intracranial bleeding – 2008 modifications)

Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): A mimic of acute myocardial infarction
Prasad et al., Am Heart J 2008; 155:408-17.

Incidence: Among 10,793 first time coronary angiography studies at Kaiser Permanente Medical Center - San Francisco, prevalence of TSCM for females was 0.9% and males 0.1%.

Estimated annual incidence in US is 7000 to 14000 cases/year.

Mortality: ~1%
Recovery: Typically complete within weeks
Recurrence: ~4% within 10 years

Community Hospital Experience With Takotsubo Syndrome in 38 Patients With Two Year Follow Up. Gupta A, Lundstrom RJ.

"False-Positive" Cardiac Catheterization Laboratory Activation for Suspected ST-Segment Elevation Myocardial Infarction

1345 Patients over 3.5 Years
1335 Underwent Angiography
187 Had no Culprit CAD

TSCM = 27%

D Larson, K Menssen, S Sharkey, et al.
JAMA, 2007;298(23):2754-2760

Table 2. Etiologies of False-Positive Cardiac Catheterization Laboratory Activation in Patients Without a Culprit Artery (n = 187)

<table>
<thead>
<tr>
<th>Etiologies by Biomarker Results</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative biomarker results (n = 123)</td>
<td></td>
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<tr>
<td>Early repolarization</td>
<td>25</td>
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<tr>
<td>Non-diagnostic electrocardiogram</td>
<td>21</td>
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<tr>
<td>Pericarditis</td>
<td>20</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>20</td>
</tr>
<tr>
<td>Left bundle-branch block</td>
<td>11</td>
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<tr>
<td>Left-ventricular hypertrophy</td>
<td>8</td>
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<tr>
<td>Vasaapasm</td>
<td>4</td>
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<tr>
<td>Tachycardia related</td>
<td>3</td>
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<tr>
<td>Right bundle-branch block</td>
<td>3</td>
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<tr>
<td>Pecardialair</td>
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<tr>
<td>Brugea syndrome</td>
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<tr>
<td>Aortic dissection</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
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<tr>
<td>Positive biomarker results (n = 64)</td>
<td></td>
</tr>
<tr>
<td>Stress cardiomyopathy</td>
<td>17</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>15</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>9</td>
</tr>
<tr>
<td>ST-elevation myocardial infarction</td>
<td>9</td>
</tr>
<tr>
<td>Infection-endocarditis/syndrome</td>
<td>4</td>
</tr>
<tr>
<td>Left bundle-branch block</td>
<td>4</td>
</tr>
<tr>
<td>Non-ST-elevation myocardial infarction</td>
<td>2</td>
</tr>
<tr>
<td>Pulmonary embolus</td>
<td>2</td>
</tr>
<tr>
<td>Aortic neoplasm</td>
<td>1</td>
</tr>
<tr>
<td>Severe aortic stenosis</td>
<td>1</td>
</tr>
<tr>
<td>Drug overdose</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
</tr>
</tbody>
</table>
Complications Associated with Takotsubo Stress Cardiomyopathy

- Left heart failure and pulmonary edema
- Cardiogenic shock
- Dynamic intraventricular obstruction with left ventricular intracavitary pressure gradient
- Mitral regurgitation from chordal tethering and systolic anterior motion
- Ventricular arrhythmias
- Left ventricular mural thrombus and thromboembolism
- Left ventricular free-wall rupture
- Death

Systematic Review: Transient Left Ventricular Apical Ballooning: A Syndrome That Mimics ST-Segment Elevation Myocardial Infarction
DL 64y female hospital ward clerk with abrupt onset of chest pain and dyspnea while rushing to meet son at airport. No CV disease history. Troponin-I 44.6 ng/ml. Cardiogenic shock required IABP.
Echocardiogram at Admission

Echocardiogram 2 Months Later

June, 2001                                   September, 2004

TSCM Recovery of Left Ventricular Systolic Function

Etiologies Considered in TSCM

- Epicardial coronary spasm superimposed on mild CAD with or without thrombosis
- Angiographically overlooked coronary atherosclerosis
- IVUS advocated
- Microvascular vasomotor spasm with or without thrombosis
- Endothelial dysfunction
- Direct catecholamine injury to myocytes
Adrenoceptor Polymorphisms and the Risk of Cardiac Injury and Dysfunction After Subarachnoid Hemorrhage

**Hypothesis:** Cardiac abnormalities after subarachnoid hemorrhage (SAH) may be caused by catecholamines. Adrenoceptor polymorphisms resulting in greater catecholamine sensitivity would be associated with an increased risk of cardiac injury.

**Results:** The combination of the βAR 389 CC and the α2AR deletion genotypes resulted in a marked increase in the odds of developing a reduced LVEF (OR 10.3, P<0.033). N=182 SAH patients.

**Conclusions:** Genetic polymorphisms of adrenoceptors are associated with an increased risk of cardiac abnormalities after SAH. These data support the hypothesis that cardiac dysfunction after SAH is a form of neurocardiogenic injury.

Zaroff, Pawlikowska, … Young; Stroke. 2006;37:1680-1685.

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Neurohumoral Features of Myocardial Stunning Due to Sudden Emotional Stress


**Endomyocardial biopsy:** Mononuclear infiltrates and contraction-band necrosis.

**Catecholamine levels:** Markedly higher with stress induced cardiomyopathy than myocardial infarction (P<0.005 for all comparisons).

**Conclusions:** Emotional stress can precipitate severe, reversible left ventricular dysfunction in patients without coronary disease. Exaggerated sympathetic stimulation is probably central to the cause of this syndrome.

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Cardiac Magnetic Resonance Imaging at Presentation

**Takotsubo Stress Cardiomyopathy**  **Anterior Myocardial Infarction**

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Regional Differences in Response to High Catecholamine Levels

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

Cardiac Adrenergic Single Nucleotide Polymorphisms in Takotsubo Stress Cardiomyopathy

No Cal Kaiser Permanente, SF/DOR
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- Ezra Amsterdam MD
- Jonathan Ko MD

University of California, Fresno
- Application Pending
- Dr. Bajwa

Takotsubo Stress Cardiomyopathy

Cohort = 332 Patients
- Females = 306 (92%)
- Males = 26 (8%)
- F : M = 13 : 1

Age 32 - 91 Yrs, Mean = 66 Yr, Median = 67 Yr
- 91% > 50 years age

Race / Ethnicity
- Caucasian 74%
- African American 11%
- Asian 8%
- Latin Am 5%
- Pacific Islander < 1%
- (Missing or Other 102)

Acute Emotional Triggers of TSCM

- Panic attack during public speaking
- Dispute with MD over medication
- Son diagnosed with cong. heart disease
- Arrest and incarceration of son
- Her cat died
- Domestic altercation
- Death of family member
- Identified body of murdered son
- Robbed at gunpoint in hospital garage
- Argument with salesperson
- Verbal assault at work
- Hosting a fund raising charitable event
- Public speaking at church group

- Burst pipe flooded apartment
- Motor vehicle accident
- Husband died in her arms
- Watched her home burn down
- Dispute with son over rental property
- Surprise 55th anniversary party speech
- Fight with husband over finances
- Daughter’s bicycle stolen
- Angry conversation
- Argument with patrons at a coin show
- Informed of her husbands sudden death
- Death of his dog

Medical Triggers of TSCM

- COPD decompensation
- Blood donation, symptoms within 1 hr
- ? Severe repetitive eructation
- Overdose, mechanical ventilation
- ETT Stress echocardiogram
- Hospitalized with urosepsis
- Pneumonia
- GI Bleed, Hct 20%
- Urosepsis
- Traumatic intubation ventilation
- Pneumonia
- Pan attack at pericardiocenteisis
- Pericardiocentesis
Physical Exertion Triggers of TSCM

- A long exhausting drive
- Exhausted during strenuous hike
- Strenuous work-out in gym
- Triathlon competition
- Sexual stimulation

Triggers of Takotsubo Stress Cardiomyopathy, Males

- 63% of females had emotional triggering events
  - Negative acute stress 71%
  - Negative chronic stress 25%
  - Positive acute stress 3%

- 37% of females had physical triggering events
  - Medical stress 51%
  - Exertion related stress 18%

Stephanie Wong, et al. KPMC-SF

Triggers of Takotsubo Stress Cardiomyopathy, Females

- 37% of females had physical triggering events
  - Medical stress 51%
  - Exertion related stress 18%

Stephanie Wong, et al. KPMC-SF

Single Nucleotide Polymorphisms Suspect in Takotsubo Stress Cardiomyopathy

<table>
<thead>
<tr>
<th>Gene</th>
<th>Rationale for protein</th>
<th>Single Nucleotide Polymorphism</th>
<th>Rationale for SNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>β1AR</td>
<td>Modules cardiac</td>
<td>1135C&gt;G</td>
<td>† response to β1-agonist stimulation³</td>
</tr>
<tr>
<td>β1AR</td>
<td></td>
<td>145A&gt;G</td>
<td>† response to β1-agonist stimulation³</td>
</tr>
<tr>
<td>β2AR</td>
<td></td>
<td>460&gt;G</td>
<td>Associated with long QT syndrome. SAH associated with QT &amp; T-wave³</td>
</tr>
<tr>
<td>β2AR</td>
<td></td>
<td>79C&gt;G</td>
<td></td>
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<tr>
<td>c-2AR</td>
<td></td>
<td>-128C&gt;T</td>
<td>† risk of CM, synergistically with Arg188Ileβ1AR³</td>
</tr>
<tr>
<td>AKAP</td>
<td></td>
<td>D-1448</td>
<td>heart rate variability³</td>
</tr>
<tr>
<td>c-2AR</td>
<td></td>
<td>-128C&gt;T</td>
<td>OD (homozygous deletion) genotype assoicated with risk of MI and SCF²</td>
</tr>
<tr>
<td>CD1D</td>
<td>Metabolites</td>
<td>Val56Met</td>
<td>VAL variant associated with lower risk of MI and HTN²³</td>
</tr>
<tr>
<td>SLC38A4, 5-HT1B</td>
<td>SHF transports</td>
<td>Insertion/Deletion: 469byG5</td>
<td>Moderates relationship of stress to anxiety, depression, and memory function²³</td>
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<tr>
<td>β2AR</td>
<td>Modules cardiac</td>
<td>Top644G</td>
<td>ArgFl associated with adverse cardiac events in females without obstructive CAD³⁴</td>
</tr>
<tr>
<td>ABCN1</td>
<td></td>
<td>5674</td>
<td>Associated with an increase in adenyly cyclase and beta-adrenergic mediated vascular reactivity²⁵</td>
</tr>
</tbody>
</table>
The “Brain–Heart” Connection

Research underway with Dr. Stephanie Wong:
Behavioral problems / Emotional illness
Personality types / Stress coping mechanisms
Left- and right-handedness

Future research topics:
Familial genetics
Coronary vasomotor and endothelial function
Sympathetic nervous system function
Functional MRI of the brain during stress

?? National Registry

Treatment of TSCM, Acute Episode

Supportive Care: Hemodynamic and respiratory support, anxiety relief and pain relief

Avoid: Alpha-adrenergic agonists (Neosynephrine, Levophed), Beta-adrenergic agonists (isoproterenol, dobutamine, dopamine)

Consider: Intra-Aortic Balloon Pump use, alpha-blockers (prazosin), combined alpha- and beta-blockers, anticoagulation if apical thrombus is present

Treatment of TSCM, Chronic Care

? Anticoagulation
? Estrogen
? Beta-blockers
? Combined alpha- and beta-blockers
? Stress management

Nobody really knows!

Long Term Prognosis with TSCM

Overall Excellent
Acute mortality ~1%
Recurrence rate ~4% / 10 years
LV Functional Recovery Complete within Weeks

Broken Heart >> Infarcted Heart!
Natural History and Expansive Clinical Profile of Stress (Tako-Tsubo) Cardiomyopathy

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Barry J. Maron, MD
Minneapolis, Minnesota and Boston, Massachusetts

Objectives
This study was designed to define more completely the clinical spectrum and natural history of stress cardiomyopathy (SC) beyond the acute event.

Background
Stress cardiomyopathy is a recently recognized condition characterized by transient bizarre dyskinesis with non-ischemic etiology.

Methods
Clinical profile and outcome were prospectively assessed in 126 consecutive SC patients.

Results
Patients were predominantly women (n = 120; 95%), but 6 were men (5%). Ages were 32 to 84 years (mean age 61 ± 13 years); 51 (39%) were <55 years of age. In 123 patients (97%), SC was precipitated by intense emotional (n = 64) or physical (n = 67) events, including 22 associated with sympathomimetic drugs or medical surgical procedures. In other patients (19%), SC had a percutaneous stress trigger. Twenty-two patients (18%) were taking beta-blockers at the time of SC events. Three distinct ventricular contraction patterns were defined by cardiovascular magnetic resonance (CMR) imaging: the “cavus” pattern with mild-to-moderate apical akinesia, the “conus” pattern with a normal apical motion, and the “systolic stunning” pattern with slight hypokinesis of the apical myocardium.

Conclusions
In this large SC cohort, the clinical spectrum was heterogeneous with about one-third either male, >50 years of age, without a stress trigger, or with in-hospital death, nodal tamponade, ventricular arrhythmia, or delayed normalization of ejection fraction. Beta-blockers were often used prophylactically and SC was a marker for increased cardiovascular mortality. These data support expanded management and surveillance strategies including CMR imaging and early recognition for arrhythmias.

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References