Takotsubo Cardiomyopathy and Other Effects of Anxiety on Cardiac Physiology

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Ms. H

68 yo F with no prior cardiac history presents to Urgent Care with 7/10 SSCP. Sudden onset 45 minutes prior, when carrying a mattress. +SOB and diaphoresis.

PMH: hyperlipidemia, depression

102/64, HR 106, 92-94% on RA
Cath
"Pt states that she has been under more emotional stress recently - she ran into one of her daughters a couple weeks ago and has subsequently been recalling bad memories from her marriage (pt is estranged from her ex-husband and both daughters). She follows closely with mental health services/psych and had an appt scheduled for tomorrow."
Takotsubo Cardiomyopathy

• Aka stress-induced cardiomyopathy, apical ballooning or broken heart syndrome
• Mimics acute coronary syndrome (ECG changes, chest pain and troponin elevation)
Types

- Takotsubo type
- Reverse takotsubo type
- Mid-ventricular type
- Localized type

Diagram showing different types of Takotsubo cardiomyopathy.
Case reports
Revised Mayo criteria

1. Transient hypokinesis, dyskinesis or akinesis of the LV mid-segments +/- apical involvement, extending beyond a single vascular distribution; a stressful trigger is often, but not always, present

2. Absence of obstructive coronary disease

3. New ECG abnormalities (ST segment elevation or T wave inversion) or modest elevation in troponin

4. Absence of pheochromocytoma or myocarditis

Cardiac Biomarkers

NTproBNP
- TCM
- STEMI

TnI
- TCM
- STEMI

NTproBNP/TnI
- TCM
- STEMI

International Takotsubo Registry

- 90% female
- Typically Caucasian or Asian
- Physical triggers more common than emotional (36% vs 28%), but 29% with no clear trigger
- Higher rates of neurologic or psychiatric disorders compared to ACS patients
- Lower incidence of traditional risk factors

Stressors

• Emotional
  – Death of a loved one
  – Bad financial news
  – Legal problems
  – Natural disasters
  – Motor vehicle collisions

• Physical
  – Exacerbation of chronic medical illness
  – Newly diagnosed significant medical condition
  – Surgery
  – ICU stay
  – Use or withdrawal from illicit drugs
Stressors

- Physical stressor: exercise, car accident, mechanical fall
- Non-cardiac surgery/medical procedure: cholecystectomy, dental procedure, intubation
- Natural disaster: earthquake, hurricane
- Emotional triggers: death of loved one, divorce, financial loss, violent argument, diagnosis of serious medical condition
- Panic attack/fear: claustrophobia, public speaking
- Onset of disease: flu, atrial fibrillation, seizure, subarachnoid haemorrhage

Takotsubo cardiomyopathy
Catecholamine hypothesis

- Serum catecholamine levels 2-3 times higher in TCM than in patients with MI (20 times normal)
- Iatrogenic administration of catecholamines (epinephrine) can trigger the syndrome
- In a rat model, the syndrome was prevented by blocking the effects of epinephrine on the heart

*NEJM 2005;352:539-48.*
*Circ 2012;126:697-70.*
Mechanisms

Catecholamine Surge

- Direct myocyte injury
- Abnormal free fatty acid metabolism and glucose uptake
- Coronary vasospasm or multi-vessel spasm
- Coronary microvascular/endothelial dysfunction
- Cardiac neuronal dysfunction/sympathetic hyperactivity

Takotsubo Cardiomyopathy
Why the apex?

- Highest density of $\beta_2$ARs at the apex
- Increased apical responsiveness to epinephrine

Why women?

- Predisposition towards microvascular disease or dysfunction
- Tendency towards HPA disruption?
- Loss of estrogen
  - Ovariectomized rats have a greater physiologic response to stress
  - Decreased NO production
Treatment

• Supportive care
  – Oxygen
  – Anticoagulation
  – Beta-blockers
  – Cessation of any sympathomimetics
  – Mechanical support for cardiogenic shock
Prognosis

• Most common complication is CHF (20%)
• 5% with LV thrombus
• 95% with complete recovery within 4-8 weeks
• Recurrence in 3.5 – 10% of patients
• In-hospital mortality 1-5%
Holter during earthquake
Physiologic Effects of Acute Stress

- Loss of nocturnal dip in BP
- Increase in blood viscosity
  - Increase in hematocrit
  - Increase in markers of procoagulant activity (fibrinogen, vWF and D-dimer)
- Increase in thromboembolic events
  - Pulmonary embolism
  - Cardiovascular death

Math = Mental Stress

Typical vs Atypical Chest Pain

1. Substernal chest discomfort
2. Provoked by exertion or emotional stress
3. Relieved by rest or NTG
Mental-stress induced ischemia predicts mortality

\( n=196 \)

\[ \text{Years of Follow-up} \]

\[ \text{Cardiac Wall Motion - Speech Test: } \]

- Normal
- Abnormal

\[ \text{% Dead} \]

\[ 0, 5, 10, 15, 20, 25 \]

\[ 0, 1, 2, 3, 4, 5, 6 \]
Mental stress vs exercise

- Increases SBP to a degree similar to exercise
- Change in BP occurs more rapidly
- HR increases less than with exercise
- Produces higher epinephrine response than exercise
- May reduce myocardial oxygen supply
“I’m going to take your blood pressure, so try to relax and not think about what a high reading might mean for your chances of living a long, healthy life.”
Arrhythmias

- Via ischemia or directly via sympathetic arousal
- Morning hours, Mondays
- Increased ectopy and arrhythmia in MDs on call
- Stress facilitates the induction of VT in animals
- Mental stress made induced VT faster and more difficult to terminate
- All patients with increase in NE >50% required shock to terminate

*Circ* 2000;101(2):158-64.
Ventricular tachyarrhythmia triggering ICD therapy

Similar increase (2.8-fold) also seen in Florida

**INTERHEART**

<table>
<thead>
<tr>
<th>Stress at work (n=12813)</th>
<th>Number of cases (%)</th>
<th>Number of controls (%)</th>
<th>Odds ratio (99% CI)</th>
<th>PAR (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>1138 (21.0%)</td>
<td>1768 (23.9%)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Some of the time</td>
<td>2499 (46.1%)</td>
<td>3923 (53.1%)</td>
<td>0.95 (0.84–1.08)</td>
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</tr>
<tr>
<td>Several periods</td>
<td>1249 (23.0%)</td>
<td>1324 (17.9%)</td>
<td>1.38 (1.19–1.61)</td>
<td></td>
</tr>
<tr>
<td>Permanent</td>
<td>540 (10.0%)</td>
<td>372 (5.0%)</td>
<td>2.14 (1.73–2.64)</td>
<td>9% (1–18)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stress at home (n=24767)</th>
<th>Number of cases (%)</th>
<th>Number of controls (%)</th>
<th>Odds ratio (99% CI)</th>
<th>PAR (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>4086 (36.8%)</td>
<td>5343 (39.2%)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Some of the time</td>
<td>5361 (48.2%)</td>
<td>6873 (50.4%)</td>
<td>1.05 (0.97–1.13)</td>
<td></td>
</tr>
<tr>
<td>Several periods</td>
<td>1288 (11.6%)</td>
<td>1179 (8.6%)</td>
<td>1.52 (1.34–1.72)</td>
<td></td>
</tr>
<tr>
<td>Permanent</td>
<td>384 (3.5%)</td>
<td>253 (1.9%)</td>
<td>2.12 (1.68–2.65)</td>
<td>8% (4–12)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>General stress* (n=24767)</th>
<th>Number of cases (%)</th>
<th>Number of controls (%)</th>
<th>Odds ratio (99% CI)</th>
<th>PAR (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>2777 (25.0%)</td>
<td>3688 (27.0%)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Some period, home or work</td>
<td>5352 (48.1%)</td>
<td>7193 (52.7%)</td>
<td>1.05 (0.96–1.14)</td>
<td></td>
</tr>
<tr>
<td>Several periods, home or work</td>
<td>2139 (19.2%)</td>
<td>2183 (16.0%)</td>
<td>1.45 (1.30–1.61)</td>
<td></td>
</tr>
<tr>
<td>Permanent, home or work</td>
<td>851 (7.7%)</td>
<td>584 (4.3%)</td>
<td>2.17 (1.84–2.55)</td>
<td>12% (7–17)</td>
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</tbody>
</table>

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<thead>
<tr>
<th>Financial stress (n=24767)</th>
<th>Number of cases (%)</th>
<th>Number of controls (%)</th>
<th>Odds ratio (99% CI)</th>
<th>PAR (99% CI)</th>
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</thead>
<tbody>
<tr>
<td>Little or none</td>
<td>4872 (43.8%)</td>
<td>6628 (48.6%)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>4625 (41.6%)</td>
<td>5361 (39.3%)</td>
<td>1.19 (1.11–1.29)</td>
<td></td>
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<tr>
<td>Severe</td>
<td>1622 (14.6%)</td>
<td>1659 (12.2%)</td>
<td>1.33 (1.19–1.48)</td>
<td>11% (7–14)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stressful life events (n=24767)</th>
<th>Number of cases (%)</th>
<th>Number of controls (%)</th>
<th>Odds ratio (99% CI)</th>
<th>PAR (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>6425 (57.8%)</td>
<td>8528 (62.5%)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2904 (26.1%)</td>
<td>3349 (24.5%)</td>
<td>1.23 (1.13–1.34)</td>
<td></td>
</tr>
<tr>
<td>2 or more</td>
<td>1790 (16.1%)</td>
<td>1771 (13.0%)</td>
<td>1.48 (1.33–1.64)</td>
<td>10% (8–13)</td>
</tr>
</tbody>
</table>

Stress = “feeling irritable, filled with anxiety or having sleeping difficulties as a result of conditions at work or at home”

Marital and work stress

![Graph showing relative risk for all-cause death by number of different work stressors.]

n=574

When was your last stress test?

Well, I went to work yesterday.
Chronic stress

- Blunted baroreflex sensitivity
- Increased atherogenesis in animal models
- Endothelial injury and platelet accumulation
- Increased levels of fibrinogen, D-dimer and inflammatory cytokines in caregivers
- Primed to hyper-respond to stressors
DBP response to stress

![Graph showing mean DBP pressor response for African American and Caucasian American participants with high and low perceived discrimination.](image)
Meditation for CHD

- Decrease in SBP and HR
- Decrease in anger expression

Stress reduction for secondary prevention

Clinical event = all-cause mortality, MI, CVA/TIA, cardiac/peripheral intervention or unstable angina requiring hospitalization

Circ 2016;133:1341-1350.
Stress Reduction Kit

Directions
1. Place kit on FIRM surface
2. Follow directions in circle of kit
3. Repeat step 2 as necessary, or until unconscious
4. If unconscious, cease stress reduction activity
Chest pain

- Common symptom: reported in 12-16% of people
- 35% seek care for their pain
- 83% are evaluated with further testing
- Only 6% lead to an organic diagnosis
- ER use is higher among pts without significant CAD
- Anxiety disorders are particularly prevalent
- Panic disorder may account for 25% of pts who present to the ER with CP

Physical Symptoms of Anxiety Disorder

- Dizziness, decreased sex drive, irritability
- Increased muscle tension
- Rapid breathing & breathlessness
- Heart palpitations
- Chest pain
- Increased blood pressure
- Nausea or diarrhea
- Numbness
- Tremors
- Chills / hot flashes
- Weakness

**AM I HAVING A HEART ATTACK?**

IN WOMEN, HEART ATTACK SYMPTOMS ARE NOT ALWAYS DRAMATIC. HERE ARE COMMON SIGNS:

- Cold sweat
- Jaw pain
- Shortness of breath (with or without chest discomfort)
- Pressure in the chest
- Nausea or vomiting
- Pain or discomfort in one or both arms
- Back pain

IF YOU HAVE ANY OF THESE SIGNS, DON'T WAIT MORE THAN FIVE MINUTES BEFORE CALLING FOR HELP. CALL 911 AND GET TO A HOSPITAL RIGHT AWAY.

SOURCE: AMERICAN HEART ASSOCIATION
Anxiety loop from h...
CP in Panic disorder

- Chest pain occurs in 22-70% of panic attacks
- Decreased HR variability, higher HR
- Mechanisms: MSK, esophageal, psychiatric, coronary

- More concerned about pain
- More convinced that they have disease
- More phobic about disease and death
- Decreased QOL, increased health care utilization
Panic Disorder

- Associated with increased:
  - Hypertension
  - Microvascular angina
  - Idiopathic cardiomyopathy
  - Sudden cardiac death
  - Overall cardiovascular mortality

- Studies limited by lack of small #s of patients and lack of control for comorbid conditions
Diagnosis

- Of 845 pts presenting to the ED with CP, 67 (8%) explicitly attributed their CP to “stress” or “anxiety”
- None (0/67) were diagnosed with anxiety
- Similar radiation exposure and associated costs
Screening test?

PHQ Panic

In the last 4 weeks, have you had an anxiety attack - suddenly feeling fear or panic?  
Yes  No

[if “a.” above is checked “No” do not present subsequent PHQ Panic Question. If “Yes” continue with Questions]

b. Has this ever happened before?  
Yes  No
c. Do some of these attacks come suddenly out of the blue; that is, in situations where you don’t expect to be nervous or uncomfortable?  
Yes  No
d. Do these attacks bother you a lot or are you worried about having another attack?  
Yes  No

Think about your last bad anxiety attack

a. Were you short of breath?  
Yes  No
b. Did your heart race, pound, or skip?  
Yes  No
c. Did you have chest pain or pressure?  
Yes  No
d. Did you sweat?  
Yes  No
e. Did you feel as if you were choking?  
Yes  No
f. Did you have hot flashes or chills?  
Yes  No
g. Did you have nausea or an upset stomach, or the feeling that you were going to have diarrhea?  
Yes  No
h. Did you feel dizzy, unsteady, or faint?  
Yes  No
i. Did you have tingling or numbness in parts of your body?  
Yes  No
j. Did you tremble or shake?  
Yes  No
k. Were you afraid you were dying?  
Yes  No

Low:  
“No” to the first question  
Not moderate or high

Moderate:  
“Yes” + 1 of b-d + 3 of a-k

High:  
“Yes” + b, c & d + 4 of a-k  
Sensitivity of 75%  
Specificity of 95%

JAMA 1999;282:1737-44.
Treatment

- Benzodiazepines reduce anxiety, pain and cardiovascular activation
- Amplify GABA through the CNS and act peripherally to reduce catecholamines
- Treats both non-cardiac and cardiac CP
- Safe and well-tolerated, with rapid onset
- Risk of dependence is minimal when prescribed on a short-term basis
- Lorazepam 0.5-1 mg prn

Summary

• Acute and chronic stress can lead to:
  – Left ventricular contractile dysfunction
  – Myocardial ischemia
  – Cardiac arrhythmia
  – Chest pain
  – Increased risk for cardiovascular events

• Via the SNS and neural-hematopoietic-arterial axis

• Stress management strategies can lead to improved outcomes in addition to improved QOL

• Improved diagnosis of anxiety in the ER may be the first step in decreasing cost and recivitism
Thank you

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