Troponin elevations in the critically ill
What do they mean?

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Disclosures

• I have no disclosures
Interaction between thin (actin) and thick (myosin) filaments
Cardiac troponins

- Sensitive and specific biomarkers of myocardial injury
- Monoclonal antibody assays: cTnI & cTnT
- New generation of HS assays has reduced the limit of detection by another 10 to 100 fold
- Unclear excretion pathways
Universal definition of MI - 2007

• ↑ or ↓ pattern of cTn, with at least 1 value exceeding 99th percentile of normal population

• Rise in cTn must be accompanied by
  – Symptoms suggesting myocardial ischemia, with at least 1 additional factor such as:
  – ECG changes or,
  – Imaging evidence of new loss of viable myocardium or new regional WMA

Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction
In ICU patients, non-coronary cTn rises most commonly associated with…

- Sepsis
- Respiratory failure
- CKD
- PE
- Heart failure
- Stroke
- Atrial fibrillation
Elevation of cTn in the absence of overt ischemic heart disease...

- Cardiac contusion
- Ablation, pacing, cardioversion, myocardial biopsy
- Congestive heart failure
- Aortic dissection, aortic valve disease, hypertrophic CM
- Tach- or brady-arrhythmias
- Rhabdomyolysis
- PE
- Severe PH
- Renal failure
- Acute neurological disease (stroke, SAH)
- Infiltrative myocardial disease: amyloidosis, sarcoidosis, hemochromatosis, scleroderma
- Myocarditis, or myocardial extension of pericarditis or endocarditis
- Drug toxicity: adriamycin, 5-fluorouracil, herceptin, snake venoms
- Critical illness, with sepsis or respiratory failure
- Burns, especially >30% BSA
- Extreme exertion
Mechanism of cTn elevation

- Supply-demand mismatch: tachycardia, hypoxemia, reduced oxygen delivery, hypotension, vasopressors/inotropes
- ↑ cardiac filling pressures and wall stress
- Direct cardiomyocyte injury: endotoxin, cytokines, reactive oxygen radicals
- Impaired microvascular perfusion
- ? Underlying CAD
Ammann et al. ICM 2001

- Case control: 20 pts SIRS, sepsis, shock & 20 controls
- Pts with clinical ischemia excluded
- ↑ cTnI in 17 (85%) cases; 0 controls (p<.0001)
- 6 deaths, all in cTn+ group
- CAD ruled out in 10/17 cTn+
  - Autopsy in 3, Angiography in 1, Stress echo in 6

Ammann et al. JACC 2003

- 58 critically ill patients WITHOUT ACS
- 55% cTn+: higher mortality, TN-alpha, IL-6
- 72%: no flow limiting CAD on autopsy or stress-echo
• 23 observational studies; 4500 patients
• 43% (IQR 21-59%) across all patient groups
• 60% in septic patients
• 53% in medical ICUs
• 43% in mixed medical-surgical ICUs
• 32% in mixed surgical-trauma ICUs

• 70% of these patients do not have flow-limiting CAD by stress echo or post mortem exam
Elevated Cardiac Troponin Measurements in Critically Ill Patients

Wendy Lim, MD, MSc(Epid); Ismael Qushmaq, MD; P. J. Devereaux, MD, PhD(Epid); Diane Heels-Ansdell, MSc; François Lauzier, MD; Afisi S. Ismaila, MSc; Mark A. Crowther, MD, MSc(Epid); Deborah J. Cook, MD, MSc(Epid)

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martin et al, 2005</td>
<td>1081</td>
<td>2.26 (1.53-3.35)</td>
</tr>
<tr>
<td>Quenot et al, 2005</td>
<td>217</td>
<td>2.09 (1.06-4.11)</td>
</tr>
<tr>
<td>King et al, 2005</td>
<td>128</td>
<td>2.82 (0.87-9.20)</td>
</tr>
<tr>
<td>Landesberg et al, 2005</td>
<td>101</td>
<td>2.71 (1.11-7.96)</td>
</tr>
<tr>
<td>Wu et al, 2004</td>
<td>108</td>
<td>4.84 (2.05-15.09)</td>
</tr>
<tr>
<td>Baillard et al, 2003</td>
<td>71</td>
<td>6.52 (1.23-34.47)</td>
</tr>
<tr>
<td>Pooled Random Effects Estimate, P &lt; .001</td>
<td></td>
<td>2.53 (1.89-3.38)</td>
</tr>
</tbody>
</table>

Heterogeneity Test: $Q = 3.54, P = .62$  
$L^2 = 0$

Figure 2. Mortality associated with an elevated cardiac troponin (cTn) level (adjusted analysis). CI indicates confidence interval; OR, odds ratio.
Association between cTn and mortality in ICU patients

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>↑ cTn</th>
<th>Mortality cTn+</th>
<th>Mortality cTn -</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bajwa 2007</td>
<td>248 ARDS</td>
<td>35%</td>
<td>56%</td>
<td>42%</td>
</tr>
<tr>
<td>Lim 2008</td>
<td>103 MSICU</td>
<td>15%</td>
<td>27%</td>
<td>2%</td>
</tr>
<tr>
<td>Babuin 2008</td>
<td>929 MICU</td>
<td>61%</td>
<td>30%</td>
<td>12%</td>
</tr>
<tr>
<td>Vasile 2010</td>
<td>2078 Resp disease</td>
<td>42%</td>
<td>21%</td>
<td>1%</td>
</tr>
<tr>
<td>Reynolds 2012</td>
<td>663 MSICU</td>
<td>52%</td>
<td>31%</td>
<td>4%</td>
</tr>
</tbody>
</table>

All single center, 4/5 retrospective; P<.05
Elevated cTn IS an independent predictor of mortality after adjusting for other variables…

- Lim, Crit Care 2008 27.3
- Lim, J Crit Care 2009 13.8
- Vasile, Am J Med 2010 1.94
  - Adjusted OR per 1-SD increment in log cTnT 1.94; 95% CI 1.72-2.18; P .0001
- Reynolds, Br J Anaesth 2012 0.25
  - OR for survival 0.25 (0.08-0.75); P=.014
Retrospective
663 medical-surgical ICU patients
65% surgical patients, most elective
All comers, median ICU days 2, 52% MV
Used low threshold for cTn elevation
Significance of Elevated Cardiac Troponin T Levels in Critically Ill Patients with Acute Respiratory Disease

Vlad C. Vasile, MD, PhD, High-Seng Chai, PhD, Sherezade Khambatta, DO, Bekele Afessa, MD, Allan S. Jaffe, MD

• Retrospective
• >2000 pts
• 42% ↑ cTnT at admission
• Cutoff troponin 0.01
• 30-day mortality
  18.6% ↑ cTnT vs 1.5%
  P<.0001

Am J Med 2010
Sepsis and septic shock
## Association between cTn and mortality in patients with Sepsis

<table>
<thead>
<tr>
<th>Study</th>
<th>N Patients</th>
<th>N C Tn</th>
<th>cTn+</th>
<th>cTn-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spies 1998</td>
<td>26 SICU</td>
<td>69%</td>
<td>83%</td>
<td>38%</td>
</tr>
<tr>
<td>Scott 2008</td>
<td>66 SICU</td>
<td>64%</td>
<td>29%</td>
<td>21%</td>
</tr>
<tr>
<td>Choon-ngarm 2008</td>
<td>40 MICU</td>
<td>42%</td>
<td>100%</td>
<td>48%</td>
</tr>
<tr>
<td>John 2010 PROWESS</td>
<td>598</td>
<td>75%</td>
<td>32%</td>
<td>14%</td>
</tr>
<tr>
<td>Rosjo 2011 Finnsepsis</td>
<td>207</td>
<td>4&lt;sup&gt;th&lt;/sup&gt; gen: 42%</td>
<td>HS: 80%</td>
<td></td>
</tr>
<tr>
<td>Tiruvoipati 2012</td>
<td>293 MICU</td>
<td>56%</td>
<td>36%</td>
<td>15%</td>
</tr>
</tbody>
</table>
Multivariable analysis
Elevated cTn IS an independent predictor of mortality after adjusting for other variables…

• John et al, Crit Care 2010 OR 2.02
  – 598 PROWESS, severe sepsis
Multivariable analysis
Elevated cTn is **NOT** an independent predictor of mortality after adjusting for other variables…

<table>
<thead>
<tr>
<th>Predictors of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAPS 2</td>
</tr>
<tr>
<td>Septic shock</td>
</tr>
<tr>
<td>CRF</td>
</tr>
<tr>
<td>Septic shock</td>
</tr>
</tbody>
</table>

- **Brivet et al, Crit Care 2006**
  - 118 adults with sepsis/septic shock

- **Kalla Am J Med 2008**
  - 159 bacteremic patients, 43% ↑cTnI

- **Oliveira Pediatr CCM 2008**
  - 218 children with sepsis/septic shock

- **Rosjo ICM 2011**
  - 207 pts in FINNSEPSIS trial; 24 ICUs

- **Tiruvoipati 2012**
  - 293 adults with severe sepsis
Multicenter DBRCT

N=778 adults with septic shock
requiring ≥ 5 ug/min norepinephrine for 6 hours

Prospective substudy

9 centers; 120 patients: 65 VP, 56 NE

ECG and troponin prospectively
  - Baseline, 6 hours, day 2 and 4
## VASST: Troponin I and T interpretation

<table>
<thead>
<tr>
<th></th>
<th>Troponin I (mcg/L)</th>
<th>Troponin T (mcg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>≤ 0.5 No myocardial injury</td>
<td>&lt; 0.05 Normal</td>
</tr>
<tr>
<td>Weakly positive</td>
<td>0.6 – 2.3 Suggestive of myocardial injury</td>
<td>0.05 - 0.09 Borderline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.10 - 0.49 Weakly positive</td>
</tr>
<tr>
<td>Highly positive</td>
<td>&gt; 2.3 Suggestive of acute myocardial infarction</td>
<td>&gt;0.49 Positive</td>
</tr>
</tbody>
</table>

Mehta S et al. Critical Care 2013;17:R117
VASST - patients with elevated troponin

Mehta S et al. Critical Care 2013;17:R117
<table>
<thead>
<tr>
<th></th>
<th>Normal (N=72)</th>
<th>Weakly positive (N=30)</th>
<th>Highly positive (N=18)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (median)</td>
<td>63</td>
<td>68</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>Male, N (%)</td>
<td>51 (71)</td>
<td>22 (73)</td>
<td>12 (67)</td>
<td></td>
</tr>
<tr>
<td>Surgical patient, N (%)</td>
<td>34 (47)</td>
<td>8 (27)</td>
<td>7 (39)</td>
<td></td>
</tr>
<tr>
<td>APACHE II</td>
<td>28 (7.6)</td>
<td>30 (6.6)</td>
<td>32 (8.6)</td>
<td></td>
</tr>
<tr>
<td>Preexisting conditions N (%)</td>
<td></td>
<td></td>
<td></td>
<td>.04</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>6 (8)</td>
<td>8 (27)</td>
<td>3 (17)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>14 (19)</td>
<td>9 (30)</td>
<td>3 (17)</td>
<td></td>
</tr>
<tr>
<td>New organ failure at randomization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, N (%)</td>
<td>66 (92)</td>
<td>25 (83)</td>
<td>16 (89)</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>49 (68)</td>
<td>21 (70)</td>
<td>14 (78)</td>
<td></td>
</tr>
<tr>
<td>Hematology/coagulation</td>
<td>17 (24)</td>
<td>8 (27)</td>
<td>7 (39)</td>
<td></td>
</tr>
<tr>
<td>Neurological</td>
<td>20 (28)</td>
<td>14 (47)</td>
<td>5 (28)</td>
<td></td>
</tr>
<tr>
<td>Clinical MI, N (%)</td>
<td>0 (0)</td>
<td>2 (7)</td>
<td>3 (17)</td>
<td>.004</td>
</tr>
<tr>
<td>28 day mortality, N (%)</td>
<td>30 (42)</td>
<td>12 (41)</td>
<td>8 (44)</td>
<td></td>
</tr>
<tr>
<td>90 day mortality, N (%)</td>
<td>40 (56)</td>
<td>14 (48)</td>
<td>8 (44)</td>
<td></td>
</tr>
</tbody>
</table>
VASST – cTn not associated with mortality

- No differences in troponin or ECGs between VP and NE groups

- Multivariable analysis
  - cTn not associated with mortality
  - APACHE II associated with 28-day mortality
    OR 1.07, 95% CI 1.01-1.14, p=0.033
  - More severe shock moderately associated
    OR 2.17, 95% CI 0.92-5.11, p=0.076

Mehta S et al. Critical Care 2013;17:R117
Sepsis – why are the results heterogeneous?

• Underpowered
• Heterogeneity of patients
  – Sepsis vs septic shock
  – Surgical vs medical
  – Pts with cardiac disease included/excluded?
  – Patients with highest mortality excluded
• Selection bias in observational studies
• Timing and frequency of cTn measurement
• cTn criteria for positivity
Troponin in renal failure

• This is not a false positive!

• Unlikely that ↑cTn is the result of ↓clearance by the failing kidney

• Unlikely that kidney is responsible for cTn clearance
  – Free and bound TnT relatively large molecules (37 & 77 kDa), similar in molecular weight to albumin (60 kDa)
  – CK of similar size and is mainly cleared by RES.

• Improvement in renal function after renal transplant does not appear to alter the occurrence of elevated serum troponin

• There is no relationship between serum creatinine and overall frequency or degree of troponin elevation

• During myocardial necrosis the elimination rate and half-life of cTnl is not significantly different in patients with normal renal function or ESRD
Elevated cTn in ICUs – a Nationwide Survey

- 310 US intensivists
- Treatment for critically ill patients with elevated cTn and without typical symptoms of MI or ECG changes?

- Responses
  - ASA or clopidogrel 76%
  - Beta-blockers 69%
  - High dose statins 49%
  - LMWH or UFH 47%
  - ACEI 38%
  - Cardiology consult 73%
  - Angiogram once stable 51%

Gundre et al. CHEST 2011;140:1013A
Conclusions

• cTn elevations common
• Individual studies: mixed results
• Meta-analysis – association with mortality

What to do?
• Vigilance for objective evidence of MI
• Treat the underlying condition
• Improve myocardial oxygen supply/demand balance
Thank-you