Cardiac Markers

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Learning objectives

• Understand the pathophysiology of acute coronary syndromes and heart failure
• Understand how biochemistry of troponin and B-type natriuretic peptides
• Discuss how cardiac troponin and the natriuretic peptides are used for diagnosis and risk stratification for ACS and HF
• Understand the role of point-of-care testing for cardiac markers
Pathophysiology of acute coronary syndromes
Pathology of Coronary Syndromes

- Normal
- Fatty Streak
- Fibrous Plaque
- Atherosclerotic Plaque
- Plaque Rupture/Fissure & Thrombosis

Clinically Silent
Stable Angina
Increasing Age
Unstable Angina
Myocardial Infarction
Sudden Death
Increasing Age
Rupture of a coronary artery

- thin fibrous cap
- site of plaque rupture
- lipid-rich ‘gruel’
- non-occlusive thrombi
Pathophysiology of acute coronary syndrome

The Pathophysiologic Continuum of AMI

- Plaque Rupture
- Intracoronary Thrombus
- Reduced Blood Flow
- Myocardial Ischemia
- Myocardial Necrosis

Classical biochemical markers (CK-MB)
ECG: St segment elevation
Biochemical events after AMI

- Coronary artery occlusion
- Myocardial ischemia
- Anoxia
- Lack of collateral blood flow
- Reversible damage
- Irreversible damage
- Cell death & tissue necrosis

ATP pump failure
  - Leakage of ions, e.g., potassium

Accumulation of metabolites
  - Leakage of metabolites, e.g., lactate

Membrane damage
  - Leakage of enzymes, e.g., LDH
Route of clearance following AMI

Ions

Metabolites

Proteins

Rapid coronary artery drainage

Slow lymphatic drainage

Systemic circulation
The term myocardial infarction should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis for myocardial infarction:

- Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:
  - Symptoms of ischemia
  - ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block (LBBB))
  - Development of pathological Q waves in the ECG
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
Troponins T and I

• Proteins found in thin filament of muscle
• Early release due to cytosolic pool
• Sustained release due to myofibrils
• Cardiac troponin not released from skeletal muscles.
• Very high tissue content.
cTnT vs. cTnI

- Equivalent diagnostic utility for AMI and risk stratification
- cTnT slightly larger than cTnI (37 vs. 24 kDa) remains positive after AMI longer.
- Abnormal cTnT found more frequently in patients with chronic renal failure than cTnI due to non-ischemic myocardial damage.
Troponin superior to CK-MB

- Myocardial tissue content
- Assays for cTnT and cTnl specific to cardiac injury
- Low normal range enables use of low cutoff concentrations
- Higher myocardial tissue content
  - CK-MB: 1.4 mg/g wet weight
  - cTnl: 6.0 mg/g wet weight
  - cTnT: 10.8 mg/g wet weight
Detection of minor damage: pre-PCI
Detection of minor damage: post-PCI

Side branch occlusion
Troponin after angioplasty

<table>
<thead>
<tr>
<th>Class</th>
<th>No. Cases</th>
<th>Thrombus or Sidebranch occ.</th>
</tr>
</thead>
<tbody>
<tr>
<td>-Tn, -MB</td>
<td>44 (55%)</td>
<td>NA</td>
</tr>
<tr>
<td>-Tn, +MB</td>
<td>0 (0%)</td>
<td>NA</td>
</tr>
<tr>
<td>+Tn, -MB</td>
<td>13 (16%)</td>
<td>9</td>
</tr>
<tr>
<td>+Tn, +MB</td>
<td>23 (23%)</td>
<td>NA</td>
</tr>
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</table>
CK-MB, myoglobin, and cTnl
Troponin and CK-MB for reinfarction
Point-of care testing for cardiac markers
POCT for cardiac markers

• Whole blood platforms.
• Quantitative and qualitative assays available
• Can significantly reduce assay TAT.
• Precision and sensitivity less than central laboratory platforms
“When a central laboratory is used to measure biochemical cardiac markers, results should be available within 60 minutes and preferably within 30 minutes.”
Does cardiac POCT reduces TATs?

<table>
<thead>
<tr>
<th>Study</th>
<th>POCT</th>
<th>Central lab</th>
<th>Δ, ↓</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caragher et al., 2002</td>
<td>38</td>
<td>87</td>
<td>56%</td>
</tr>
<tr>
<td>Lewandrowski et al. 2003</td>
<td>17</td>
<td>110</td>
<td>85%</td>
</tr>
<tr>
<td>Collinson, et al. 2004</td>
<td>20</td>
<td>79</td>
<td>75%</td>
</tr>
<tr>
<td>McCord, et al. 2001</td>
<td>24</td>
<td>71</td>
<td>66%</td>
</tr>
<tr>
<td>Singer et al. 2005</td>
<td>15</td>
<td>83</td>
<td>85%</td>
</tr>
<tr>
<td>Mean</td>
<td>23</td>
<td>89</td>
<td>79%</td>
</tr>
</tbody>
</table>
POC testing for AMI

• STEMI: ECG, no cardiac markers needed
• NSTEMI: troponin increased dramatically, POCT adequate
• UA/NSTEMI: variability in performance of POCT devices.
Discordances from POC v central lab testing
Outcomes in relation to troponin: assay sensitivity

1. Troponin T (0.1 µg/L)
   - OR 3.20; 2.22-4.59
   - OR 1.82; 1.38-2.40
   - OR 2.26; 1.79-2.85

2. Troponin T (0.01 µg/L)
   - OR 4.55; 2.66-7.78
   - OR 3.42; 2.57-5.98
   - OR 4.29; 3.02-6.09

3. Rapid Troponin I Assay
   - OR 1.80; 1.30-2.54
   - OR 1.47; 1.12-1.93
   - OR 1.64; 1.31-2.06
Evolution: troponin cutoff concentrations
Troponin T cutpoints

cTnT

ROC AMI cutoff 0.1

10% CV limit 0.03
LOQ

99th percentile 0.01
=LOD

LOB
In the presence of a clinical history suggestive of ACS, the following are considered indicative of myocardial necrosis consistent with MI (Level of Evidence: C):

- Maximal concentration of cardiac troponin exceeding the 99th percentile of values (with optimal precision defined by total CV <10%) for a reference control group on at least 1 occasion during the first 24 h after the clinical event (observation of a rise and/or fall in values is useful in discriminating the timing of injury). “
Receiver operating characteristic curve derived

Current ESC/ACC recommendation (99th percentile) → Normal individuals → Stable angina → Unstable angina → Myocardial infarction

- Normal individuals: no injury
- Stable angina: no injury
- Unstable angina: little to moderate injury → significant injury
- Myocardial infarction: increasing

Concentration of cardiac marker

Initial strategy prior to ESC/ACC redefinition (ROC) → Strategy based on 10% CV
hsTroponin T for AMI

Includes next generation hs-cTnT
hsTnI in ED patients with chest pain

Non-diagnostic

Ischemia?

Frequency

pg/ml cTNI

0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 More

1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 More
Cardiac troponin for risk stratification of unstable angina

Risk stratification vs. cutoff
Morrow et al. JAMA 2001;286:2405-12.

181 patients out of 1821 missed when raising the cutoff to the 10% CV.
Troponin elevations without ischemia

- Trauma, burns
- Congestive heart failure
- Aortic valve disease and hypertrophic obstructive cardiomyopathy
- Hypertension and hypotension
- Postoperative noncardiac surgery patients and PCI
- Renal failure
- Critically ill patients (diabetes, respiratory failure, GI bleed, sepsis)
- Drug toxicity (adriamycin, 5-fluorouracil, herceptin, snake venoms)
- Hypothyroidism
- Abnormalities in coronary vasomotion, including coronary vasospasm
- Apical ballooning syndrome
- Inflammatory diseases (e.g., myocarditis, parvovirus, Kawasaki disease)
- Pulmonary emboli, severe pulmonary hypertension
- Infiltrative diseases (e.g., amyloidosis, hemochromatosis, scleroderma)
- Acute neurological disease, (e.g., CVA, subarachnoid bleeds)
- Rhabdomyolysis with cardiac injury
- Transplant vasculopathy
- Vital exhaustion
AMI rule out algorithm
Hamm et al. Eur Heart J. 2011;32:2999-3054
Summary for troponin

- Key element in re-definition of AMI
- Important for risk stratification for short-term adverse cardiac events
- Little difference in cTnT vs. cTnI
- Use of the 99th percentile optimizes detection of minor myocardial damage → high risk
- CK-MB and myoglobin redundant today
Natriuretic peptides
A condition where the heart is unable to supply the body with enough oxygen-rich blood to accommodate the body’s needs during exercise and at rest. As a result of decreased function body fluids may build up in the lungs and limbs.
Healthy
Heart failure
Natriuretic peptides

- The natriuretic peptides are a family of 3 related forms.
- They are increased in CHF due to enhanced atrial & ventricular synthesis.
- ANP: 28-aa peptide found in the atrium of the heart
- BNP: 32-aa peptide found in the brain and ventricles of the heart
- CNP: 22 aa peptide found in the brain and CNS
- Urodilatin: 32 aa peptide, is the renal form of ANP
Architectural Changes of the Failing Heart

<table>
<thead>
<tr>
<th>Ischemic</th>
<th>Normal</th>
<th>Decreased Blood Output</th>
</tr>
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<tbody>
<tr>
<td>Dilated Cardiomyopathy</td>
<td></td>
<td></td>
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</table>

Elliptical shape is energetically efficient.

Spherical shape not energetically efficient.

BNP released w/ wall stretching
Natriuretic peptides and vasopressin: counterbalance

Hypertension

BNP, ANP
- Vasodilatation
- Natriuresis/diuresis

Renin, aldosterone
- Vasoconstriction
- Salt/water retention
- Increase heart rate/contractility

Hypotension
Release of BNP from Cardiac Myocytes

Roche, Dade, DPC, Ortho

Abbott, Bayer, Biosite (Beckman)
NT-ProBNP vs. BNP

- For CHF patients, no difference in performance between BNP and NT-ProBNP.
- $T_{1/2}$: BNP-20 min, NT-ProBNP: 90 min (sheep).
- Cannot use BNP to monitor endogenous BNP levels during nesiritide therapy.
- NT-Pro BNP has a longer in vitro sample stability (72 h) than BNP (4 h).
BNP in apparently healthy individuals
BNP vs. NYHA Classification

Survival and the 6-min walk test (EF<45%)
6-min walk test
“Breathing Not Properly” Study

- 1586 patients presenting to the ED with shortness of breath
- Data recorded: history, physical exam, lab tests
- Initial assessment by ED physicians
- Followup assessment: 2 cardiologists with access to all tests (echos), hospital course, response to treatment, etc.
- BNP measured
BNP in Patients Without CHF, Baseline LV Dysfunction and CHF

- Non-CHF: n = 770
- CHF: n = 744
- Known LV dysfunction not acute: n = 72
BNP vs. BMI in patients with CHF
BNP in renal disease
BNP vs. EF by echocardiography

BNP in diastolic HF
BNP after CHF (EF<45%)  

Cumulative survival

Months

BNP > 73 pg/ml

BNP < 73 pg/ml

p < 0.001
ESC Heart failure guideline

Suspected heart failure

Acute onset

ECG
Chest x-ray

- Echocardiography
- BNP/NT-pro BNP

- ECG normal and NT-proBNP <300 pg/mL or BNP <100 pg/mL
- Heart failure unlikely

- ECG abnormal or NT-proBNP ≥300 pg/mL or BNP ≥100 pg/mL

Non-acute onset

ECG
Possibly chest x-ray

- Echocardiography
- BNP/NT-pro BNP

- BNP/NT-proBNP ≥125 pg/mL or BNP ≥35 pg/mL
- Heart failure unlikely

- ECG normal and NT-proBNP <125 pg/mL or BNP <35 pg/mL

If heart failure confirmed, determine aetiology and start appropriate treatment
HF case reports

• Three patients present at different times to the ED with dysnea. They are all males, aged 50-55 y and a 3-5 y hx of heart failure.
• BNP is tested daily until discharge (not recommended practice).
• Each patient is followed over the next 180 days for recurrent HF death or re-hospitalization.
Which of these patients has a better prognosis upon discharge?

*BNP Serial Testing*

- **High baseline, greatest change**
- **Lowest Baseline BNP Level**
- **Lowest Pre-discharge BNP**

**Chart Details:**
- **Patients:** Patient 1, Patient 2, Patient 3
- **Times:** Day 1, Day 2, Day 3, Day 4, Day 5, Day 6
- **Values:** 100, 300, 500, 700, 900, 1100, 1300, 1500, 1700, 1900

**Legend:**
- Patient 1: Red line and symbols
- Patient 2: Green line and symbols
- Patient 3: Yellow line and symbols

**Analysis:**
- **Patient 1** shows a significant decrease in BNP levels, indicating a better prognosis.
- **Patient 2** also shows a decrease but less pronounced than Patient 1.
- **Patient 3** has the lowest baseline and lowest pre-discharge BNP levels, suggesting a good prognosis.

**Conclusion:**
- Based on the chart, **Patient 1** and **Patient 3** have better prognoses upon discharge compared to **Patient 2**.
Heart failure outcomes

- Predischarge BNP >700 ng/L
  n=41, events=38

- Predischarge BNP 350-700 ng/L
  n=50, events=30

- Predischarge BNP <350 ng/L
  n=111, events=18

Hazard Ratios of 2nd and 3rd Versus 1st BNP Range

Follow-Up (Days)
Summary for BNP/NT-proBNP

- Widely used for diagnosis of HF in ED
- Important for risk stratification for short-term adverse cardiac events
- Little difference in BNP vs. NT-proBNP
- Utility for screening asymptomatic patients to be determined
- Utility for therapeutic monitoring of decompensated HF established
- Utility for outpatient therapeutic monitoring to be determined
Self-assessment questions

Which of the following is the recommended strategy for cutoff assignments for troponin?

A. 95\textsuperscript{th} percentile of healthy population
B. 99\textsuperscript{th} percentile of healthy population
C. Value at the assay’s 10\% CV
D. Receiver operating characteristic curve-derived cutoff
E. B and C.

Answer: The ACC/AHA Task Force has recommended the 99\textsuperscript{th} percentile for assays that have a 10\% CV or less
Self-assessment questions

Which of the following does not increase the level of BNP/NT-proBNP in a patient population who is asymptomatic for heart disease?

A. Renal insufficiency
B. Female gender
C. Subject age
D. Body mass index
E. None of the above

Answer: D. Obesity decreases BNP/NT-proBNP.
Self-assessment questions

Which is FALSE regarding point-of-care testing for troponin?

A. Current POC assays are less sensitive than the central lab.

B. Turnaround times are improved with POC.

C. Clinical studies have demonstrated improved clinical outcomes with use of POC testing.

D. POC test results are not standardized with central lab results.

E. POC test results can be used for risk stratification.

Answer: C. No such clinical trial has shown a clinical advantage of POCT.