BIOCHEMICAL CARDIAC MARKERS IN ACUTE CORONARY SYNDROME

BY DR L A GOVENDER
### PATHOPHYSIOLOGY OF MYOCARDIAL INFARCTION

#### THE PATHOPHYSIOLOGY OF ACUTE CORONARY SYNDROMES AND BIOMARKERS RELEASED INTO BLOOD

<table>
<thead>
<tr>
<th>Condition</th>
<th>Biomarker(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaque rupture</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>Intracoronary thrombus</td>
<td>P.selectin, fibrinopeptide A</td>
</tr>
<tr>
<td>Reduced blood flow</td>
<td>Myocardial perfusion imaging</td>
</tr>
<tr>
<td>Myocardial ischemia</td>
<td>Ischemia-modified albumin</td>
</tr>
<tr>
<td>Myocardial necrosis</td>
<td>Troponin, myoglobin, CK-MB <strong>(IRREVERSIBLE DAMAGE)</strong></td>
</tr>
</tbody>
</table>

- **Continuum of AMI risk**
  - Asymptomatic
  - Unstable angina
  - Myocardial Infarction

- **Acute coronary syndromes** are due to an acute or sub acute primary reduction of myocardial oxygen supply provoked by disruption of an atherosclerotic plaque associated with inflammation, thrombosis, vasoconstriction and microembolization.
- **Finite process.** (>4-6 h for necrosis to develop).
The term Acute Coronary Syndrome refers to a range of acute myocardial ischaemic states.

- Coronary Artery Diseases (CAD):
  - a continuum of increasing risk of morbidity and mortality:
    - Starts with asymptomatic CAD
    - Develops through stable and unstable angina
    - Progresses to non-Q-wave MI
    - ends in transmural MI, cardiac arrhythmia, and death
- Myocardial infarction is the terminal event in a spectrum of disease called acute coronary syndromes (ACS) and caused by acute myocardial ischemia.
PATHOPHYSIOLOGY OF MYOCARDIAL INFARCTION

Plaque disruption or erosion

Thrombus formation with or without embolisation

Acute cardiac ischaemia

No ST segment elevation

Markers of myocardial necrosis not elevated

Unstable angina

Elevated markers of myocardial necrosis

Non-ST segment elevation myocardial infarction (Q waves usually absent)

ST segment elevation

Elevated markers of myocardial necrosis

ST segment elevation myocardial infarction (Q waves usually present)

Acute coronary syndromes

Spectrum of acute coronary syndromes according to electrocardiography and biochemical markers of myocardial necrosis (troponin T, troponin I and creatine kinase MB), in patients presenting with acute cardiac chest pain

Grech, BMJ 7/6/2003 326, 259-261
AMI or unstable angina is initiated by acute plaque rupture and resulting in thrombus formation with or without embolisation. The development of infarction or ischaemia will depend on the degree of occlusion or the presence of collateral blood flow.
The role of cardiac markers in the diagnosis and treatment of patients with chest pain and suspected ACS has evolved considerably. The clinical evaluation often is limited by atypical symptoms, in most patients the initial ECG is non-diagnostic.
HISTORICAL CRITERIA FOR DIAGNOSIS OF MI (WHO, 1974)

• Triad of criteria

• Diagnosis requires Two of:
  – Severe & prolonged chest pain
  – Unequivocal ECG changes consistent with acute MI
  – Elevated serum cardiac enzymes
However, new guidelines by American College of Cardiology (ACC) and the European Society of Cardiology (ESC) have redefined AMI and focuses on the importance of cardiac markers.

**ESC/ACC AMI REDEFINED**

Revised Criteria: Acute/Evolving/ Recent MI

- Typical myocardial necrosis-associated rise & fall of Troponin or CK-MB\textsubscript{mass} (serial determinations)

  **PLUS**

- One of:
  - Clinical cardiac ischaemia (or equivalents*)
  - Q waves on ECG
  - ST segment changes indicative of ischaemia
  - Coronary artery imaging (stenosis/obstruction)

- **OR** Pathologic findings of an acute MI
This is a significant change from the WHO classification because patients who were formally diagnosed with unstable angina or minor myocardial injury are now reclassified as having acute NSTEMI.
WHAT ARE CARDIAC MARKERS?

• Located in the myocardium
• Released in cardiac injury
  – Myocardial infarction
  – Non-Q-wave infarction
  – Unstable angina pectoris
  – Other conditions affecting cardiac muscle
    (trauma, cardiac surgery, myocarditis etc.)
• Can be measured in blood samples
Size and subcellular distribution of myocardial proteins/markers determines time course of biomarker appearance in the general circulation.
PATHOPHYSIOLOGY OF ACUTE CORONARY SYNDROMES & BIOMARKER RELEASE INTO THE CIRCULATION

Coronary artery occlusion
  ↓
Myocardial ischaemia
  ↓
Anoxia
  ↓
Lack of collateral blood flow
  ↓
Reversible damage
  ↓
Irreversible damage
  ↓
Cell death and tissue necrosis

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

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

Membrane damage
  Leakage of myocardial proteins & enzymes
QUESTIONS ANSWERED BY MARKERS OF CARDIAC DAMAGE

- Rule in/out an acute MI
- Confirm an old MI (several days)
- Monitor reinfarction
- Monitor the success of thrombolysis
- Risk stratification of patients with UA

N.B. Risk stratification in apparently healthy persons not done with cardiac markers, but by measurement and assessment of cardiac RISK factors
RELEASE KINETICS OF MYOCARDIAL CELL CONSTITUENTS
BIOCHEMICAL MARKERS IN MYOCARDIAL ISCHAEMIA / NECROSIS

IN:
- CK-MB (mass)
- c.Troponins (I or T)
- Myoglobin

OUT:
- AST activity
- LDH activity
- LDH isoenzymes
- CK-MB activity
- CK-Isoenzymes
- ?CK-Total

FUTURE:
- Ischaemia Modified Albumin
- Fatty Acid binding protein
- CD40 Ligand binding protein
CK-MB ISOENZYMES

• CK-MB iso-enzymes have been biochemical indicator of choice for the diagnosis of AMI.
• Cardio-specificity of CK-MB is not 100%
• They are present in both skeletal and cardiac muscle.
• False positive elevation occurs in trauma, heavy exertion and myopathies.
• First appears 4-6 hours after symptoms onset.
• Peaks at 24 hours.
• Returns to normal in 48-72 hours.
MYOGLOBIN

Myoglobin is a heme-protein found in skeletal and cardiac muscle
It is currently the earliest marker
Rises 2-4 hours after onset of infarction
Peaks at 6-12 hours
Returns to normal within 24-36 hours
Important for ruling out MI rather than ruling in.
TROPONINS
These are regulatory proteins found in skeletal and cardiac muscles.
Three subunits are identified, namely
  Troponin I
  Troponin T
  Troponin C

CARDIAC TROPONINS

• Striated and cardiac muscle filaments consist of:
  • Actin
  • Myosin
  • Troponin regulatory complex
• Troponin complex: 3 distinct sub-units on thin filament: TnC, TnT & TnI, which regulate myosin-actin Ca-dependent interaction.
• TnT & TnI sub-units of skeletal & myocardial troponin are sufficiently different for antisera to differentiate between two tissue forms
• A fraction of total troponin is found free dissolved in the cytosol
Troponin I and T
• Troponins have high specificity for myocardial injury
• Sensitive to minor myocardial damage
• Appear 4-8 hours after symptoms onset
• Remain elevated for up to 14 days post MI
• Useful in risk stratification of patients with ACS
• Useful in identifying patients with high risk of adverse cardiac event.
TROPONINS

BIOCHEMICAL MARKERS IN ACS UNSTABLE ANGINA PECTORIS (UA)

- cTnI & cTnT are often elevated in UA without additional clinical signs (ECG) or classical laboratory signs of acute MI (raised CK-MB)
- These patients have a high risk of cardiac events
TROPONINS

BIOCHEMICAL MARKERS IN ACS RISK STRATIFICATION IN UA

Irreversible minor myocardial injury detected by TnT/I may stratify UA patients as high risk for progression to AMI
Baseline levels of troponin have been shown to predict the risk of adverse cardiac events in patients with non-ST elevation ACS.
TROPONIN AND MI DIAGNOSIS

It is estimated that about 30% of patients who present with chest pain without ST-segment elevation and would otherwise be diagnosed as having unstable angina because of a lack of CK-MB elevation actually have NSTEMI when assessed with cardiac-specific troponin assays.

JACC and Circulation 2002
Troponin can be used to efficiently categorise patients into high and low risk groups for appropriate management pathways.
TROPONINS

RISK STRATIFICATION IN ACS

Useful for:

– Selection of the site of care
  • Coronary care unit versus monitored step-down unit or outpatient setting

– Selection of appropriate therapy
  • Aggressive versus conservative therapy
  • LMW Hep / GPIIb/IIIa inhibitors can erase increased risk in patients with NSTEMI TnT elevations (Bock, 2002)
OTHER CARDIAC MARKERS

Ischaemic Modified Albumin (IMA)
IMA is a novel marker of ischaemia based on the modification of cobalt to albumin in ischaemia is currently undergoing investigation.
It is a marker sensitive for ischaemia rather than necrosis. It is detected within a few minutes, peaks at 2-4 hours and disappears within 6 hours.
WHAT IS THE BEST MARKER

• The best marker depends on the time from onset of symptoms.
• The earliest marker is myoglobin and CK-MB isoforms.
• In the intermediate period (6-24 hours) CK-MB and Troponin.
• More than 24 hours Troponins are recommended.
Cardiac markers are not necessary for diagnosis of patients who present with ischaemic chest pain or diagnostic ECG with ST elevation. Treatment should not be delayed to wait for cardiac marker results since the sensitivity is low in the first 6 hours after symptom onset.
## KINETICS OF CARDIAC MARKERS AFTER AMI

<table>
<thead>
<tr>
<th>MARKER</th>
<th>DETECTION</th>
<th>PEAK</th>
<th>DISAPPEARANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myoglobin</td>
<td>1 – 4 h</td>
<td>6 – 7 h</td>
<td>24 h</td>
</tr>
<tr>
<td>CK-MB mass</td>
<td>3 – 12 h</td>
<td>12 – 18 h</td>
<td>2 – 3 days</td>
</tr>
<tr>
<td>Total CK</td>
<td>4 – 8 h</td>
<td>12 – 30 h</td>
<td>3 – 4 days</td>
</tr>
<tr>
<td>cTnT</td>
<td>4 – 12 h</td>
<td>12 – 48 h</td>
<td>5 – 15 days</td>
</tr>
<tr>
<td>cTnI</td>
<td>4 – 12 h</td>
<td>12 – 24 h</td>
<td>5 – 7 days</td>
</tr>
</tbody>
</table>

These values represent averages.
In patients with definite or possible ACS serial evaluation of cardiac markers is essential

### Sampling FREQUENCY

<table>
<thead>
<tr>
<th></th>
<th>BASELINE</th>
<th>2-4 h</th>
<th>6-12 h</th>
<th>12-24 h</th>
<th>&gt; 24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early (isoforms, myoglobin)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Intermediate (CK-MB, Tnl, TnT)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Late (Tnl, TnT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
The recent American Heart Association guidelines for the treatment of patients with UA and NSTEMI recommends baseline sample on arrival and a repeat sample 8-12 hours after symptoms onset. Patients with negative serial marker results through the 8-12 hour period can be excluded for AMI.
ROLE OF CARDIAC MARKERS IN THERAPEUTIC DECISION IN ACS

There is little evidence that supports the use of cardiac marker as an indicator for specific therapeutic interventions, however, there are studies which confirm that appositive troponin result alone is an independent predictor of high risk and such patients may benefit from low molecular weight heparins or glycoprotein GIIB\IIIA inhibitors that markedly reduces platelet aggregation.
TROPONIN T VS TROPONIN I

From a clinical point of view, little difference exists between current generations of Troponin T and Troponin I regarding sensitivity and specificity.
USE OF CARDIAC MARKERS IN PATIENTS WITH CHEST PAIN

CK-MB_{mass} is most useful in assessing a recent vs an older MI or to confirm reinfarction (occurs in 17% of AMI’s). Repeat CK-MB_{mass} if chest pain recurs in AMI patients.

Recent work (Apple & Murakami, 2004) suggests that TnI (shorter elevation period) may be as effective and more sensitive in detecting reinfarction.
USE OF CARDIAC MARKERS IN PATIENTS WITH CHEST PAIN

Mb, CK-MB\text{mass}, Troponin \text{POSITIVE AMI}

Mb \text{ONLY POSITIVE}
\text{Possible early infarction or skeletal muscle injury}
Repeat markers
(NB importance of Mb is as a \text{Negative Predictor})

Mb + CK-MB \text{POSITIVE}
\text{Probable early infarction}
Repeat markers
A rising CK-MB $\Rightarrow$ AMI
“Washout” phenomenon – enzymes & proteins have direct vascular access when occluded coronary circulation becomes patent
• Peak concentrations earlier & at higher levels if reperfusion successful

Due to short plasma half life \((t_{1/2} = 10 \text{ min})\) Myoglobin is considered the best reperfusion marker.
GUIDELINES:
USE OF CARDIAC MARKERS IN PATIENTS WITH CHEST PAIN

TnI ≤ 0.06 ng/mL OR TnT ≤ 0.03 ng/mL
on two specimens > 6 hours apart

Unstable Angina

Tn I > 0.06 ng/mL
  TnT > 0.03 ng/mL [Elecsys]
  > 0.09 ng/mL [Reader] (0.03-0.09 equivocal)

? High risk ACS(AMI) or non-ischaemic myocardial damage depending on clinical cardiac ischaemia
  These patients require follow-up!!

Tn I > 0.5ng/mL* OR TnT >0.1 ng/mL (?>1.0 *)
“traditional” AMI

USE OF CARDIAC MARKERS IN PATIENTS WITH CHEST PAIN

ALSO FOR ASSESSMENT OF:

Intra- or post-operative AMI Troponins

MI after percutaneous coronary artery intervention Troponins (30-40% pts)

CK-MB (5-30% pts)

(compare with baseline or use 5-15 fold higher cut-off level)
NON-ISCHAEMIC CAUSES OF CARDIAC TROPONIN ELEVATION

Myocarditis / Pericarditis
Heart failure (including acute pulmonary oedema)
Hypertension
Hypotension (especially if associated with cardiac arrhythmias)
Critically-ill patients (NB diabetics)
Hypothyroidism
Cardiac trauma
Chemotherapy-induced myocardial toxicity
Heart transplant rejection
SUMMARY: ROLE OF CARDIAC MARKERS IN EVALUATION OF ACUTE CORONARY SYNDROMES:

- Key role of cTnI & cTnT in MI diagnosis
- Any Troponin level > URL = Myocardial damage

This identifies a new sub-group of high-risk, poor prognosis ACS patients

- Reason for myocardial injury needs to be determined in patients without clinical cardiac ischaemia
- ACS patients with even small elevations in cTn derive clinical benefit from early follow-up and appropriate therapy

- Serial sampling is critical for accurate diagnosis
- Do NOT discharge patients on the basis of negative results on an admission specimen
- If onset of chest pain >9-12 h before admission only Troponin is necessary
- Do not delay appropriate intervention in patients with OVERT AMI while waiting for biomarker results.
CONCLUSION

• Cardiovascular disease a continuum from UA to MI. This has required a redefinition of Myocardial Infarction.

• Cardiac Troponins now play a pivotal role in the diagnosis of AMI.

• Cardiac Troponins play an important role in the risk stratification of ACS patients

  • Elevated Troponin levels in patients without ECG changes & with normal CK-MB levels may identify patients at increased risk of cardiac events

• Although cardiac markers are useful tools in the evaluation of patients with suspected ACS, there is still no substitute for clinical judgment.

• Cardiac markers cannot be used particularly in the early hours after symptoms onset to exclude the disease reliably.

• Keep in mind other life threatening etiologies of chest pain, such as aortic dissection and pulmonary embolism for which cardiac markers have no diagnostic value.
Thank You!