CARDIAC BIOMARKERS

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INTRODUCTION

- Biomarker is a specific physical trait or a measurable biologically produced change in the body connected with a disease or health condition
- = molecular marker or signature molecule
- Cardiac biomarker is a marker of myocardial injury
- Necrotic myocytes loose membrane integrity & IC macromolecules diffuse into cardiac interstitium and ultimately into cardiac microvasculature & lymphatics and lastly drain to circulating blood

HISTORY

- 1954 SGOT (AST)
- 1955 LDH
- 1960 CPK
- 1972 CPK isoforms by electrophoresis
- 1975 CK-MB by immunoinhibition
- 1975 Myoglobin
- 1985 CK-MB mass immunoassay
- 1989 Troponin T
- 1992 Troponin I

IDEAL MARKER SHOULD HAVE

- DIAGNOSTICALLY

1. High sensitivity (detection of MI)
2. High specificity (absent in non-MI injury)
3. Rapid release at detectable concentration
4. Correlate efficiently with extent of MI
5. Long $T_{1/2}$

- ANALYTICALLY

1. High sensitivity (low detectable limit)
2. High specificity (less interference)
3. Easy, inexpensive & rapidly tested

TYPES

CARDIAC ENZYME MARKERS

1. CK
2. LDH

CARDIAC PROTEIN MARKERS

1. Myoglobin
2. Troponins
3. FA Binding Protein

PROGNOSTIC & RISK STRATIFICATION MARKERS

1. C R P
2. M P O
3. Homocysteine
4. G F R

CREATINE KINASE

- Catalyses the conversion of creatine to phosphocreatine degrading ATP to ADP
- Two subunits - *B* (brain) or *M* (muscle)
- Isoenzymes : *CK-MM, CK-BB* and *CK-MB*
- Skeletal muscle expresses *CK-MM* (98%) & *CK-MB* (1%)
- myocardium has *CK-MM* at 70% and *CK-MB* at ~30%

CK-MB

- High specificity for cardiac tissue
- Begins to rise 4-6 hours after onset of infarction
- Peaks at about 12 hours
- Returns to baseline at 48-72 hours
- Can be used to indicate early re-infarction if level normalizes and then increases again
- Lab test is for mass, not activity ; mass assays are reported to be more sensitive.

LIMITATIONS

- False positive (for MI) CK-MB seen in:
  - Significant skeletal muscle injury
  - Cardiac injury for reason other than MI
    - Cardioversion, Defibrillation
    - Blunt chest trauma
    - Cardiac & non-cardiac surgical procedures
    - Cocaine abuse
    - Severe myocarditis,

MB Index

- MB Index = CKMB x100/CK
- Rationale for using MB Index
  - Using CKMB alone (RI <5.0 ng/mL) often yields FP results
  - Combined use with MB Index helps to rule-out patients with skeletal muscle injury
- What cut-off value for MB Index to use?

L D H

- a H_2 transfer enzyme catalyzes reduction of L-lactate to pyruvate using a carrier NAD in an alkaline pH

- is a tetramer of 4 peptide chains of 2 types forming five isoenzymes

1. LD1 (H_4)
2. LD2 (H_3M)
3. LD3 (H_2M_2)
4. LD4 (HM_3)
5. LD5 (M_4)

L D H

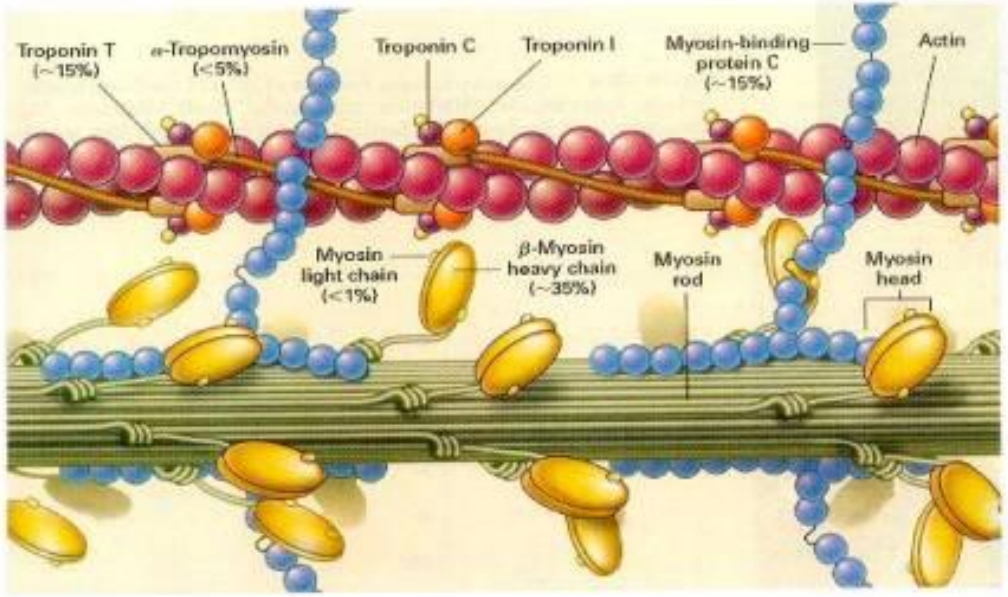
- Rises at about 10 hours
- Peaks at 24-48 hours
- Remains elevated for up to 8 days
- Pancreas, kidney, stomach tissue, red cells cardiac tissue contains LD-1 (nonspecific)
- Normal LD1/LD2 is between 0.47 – 0.74
- In myocardial injury LD1/LD2 will be > 1

A S T (S G O T)

- Used as surrogate markers of cellular damage in the past.
- Very non-specific
- Not used for assessment of myocardial damage any longer

TROPONINS

- Are sacromeric bound proieins and only a 5% free in cytoplasm
- TpC, TpT, TpI



TROPONIN C

- binds to calcium ions to produce a conformational change in TnI
- Same isoform for both skeletal & cardiac muscles
- No immunological difference bet 2
- No method to differentiate for Myocardial injury diagnosis

TROPONIN T & I

- Different isoforms for cardiac & skeletal tissue
- Require myocardial necrosis for release from sarcomere
- Early rise : 4 – 12 hours after chest pain
- Continuous release upto 10 – 14 days
- Unclear excretion pathway

TROPONIN T

- binds to tropomyosin, interlocking them to form a troponin-tropomyosin complex
- 4 isoforms
- Studies found some Troponin-T in skeletal muscle
- Re-expression of cardiac troponin T in muscles : muscle injury, myopathy, renal failure

TROPONIN I

- Cardiac isoform of trop I is only found in cardiac muscles (cTnI)
- Binds to actin in thin myofilaments to hold the troponin-tropomyosin complex in place
- < 5 % in cytosol
- Strong binding with trop C may affect assay
- Also affected by protein kinases, fibrinogen levels & heparin in sample

ADVANTAGES OF TROP

- good utility for retrospectively diagnosing AMI
- Troponin release can also be precipitated by other conditions causing myocardial damage
- Degree of elevation of Troponin value can give prognostic information
- Detectable levels indicate chronic disease even if not acute myocardial damage

Clinical Issues in New Guideline

- ↑cardiac troponin reflects myocardial injury but do not indicate its mechanism
  - Not synonymous with MI or ischemic mechanism of injury. Pursue other etiologies of myocardial injury
  - Likely reflects irreversible injury
  - ↑Tpn after heart surgery; can't differentiate injury caused by MI from procedural-induced injury

MYOGLOBIN

- Ubiquitous small-size haeme protein released from all damaged tissues.
- Increases often occur more rapidly than trop and CK.
- Not used because of its very rapid metabolism & lack of specificity for cardiac tissue.
- Increased in : Acute M I, open heart surgery, skeletal muscle damage, renal failure, severe uremia, shock & trauma

CLINICAL USES

- Rapid monitor of success of thrombolytic therapy
- Negative predictor of M I

FATTY ACID BINDING PROTEIN

- Small cytoplasmic proteins, abundant in heart muscles
- Most sensitive early cardiac marker
- < 3 hours for diagnosis
- Returns to normal in 12 – 24 hours
- Studies ongoing to further to evaluate its utility

C-REACTIVE PROTEIN

- Plasma levels can increase rapidly upto 1000 X normal level in response to acute inflammation
- + acute phase reactant
- Is an acute mediator of atherogenesis
- High-sensitivity CRP (hs-CRP) assays (i.e. Dade Behring) detect levels of CRP within the normal range, levels proven to predict future cardiovascular events.

CRP ROLE IN CV DISEASE

- Screening for cardiovascular risk in otherwise healthy people
- Predictive value of CRP levels for disease severity in pre-existing CAD
- Prognostic value in A C S
- Elevated level predicts : long term risk of first M I, Ischemic stroke

LIMITATIONS of C R P

- Low specificity
- No evidence that lowerng CRP levels decreases CV risk
- Medications like statins lower CRP levels
- No role in stable angina
- Diminished role in post-CABG & post-PCI
- Not good in prognosis of non-ST elevation ACS

MYELOPEROXIDASE

- Released by activated leukocytes at elevated levels in vulnerable plaques
- Predicts cardiac risk independently of other markers of inflammation
- Useful in triage of ACS
- Elevate in 1st two hours of ACS
- Identifies patients at increased risk of CV event in the 6 months following a negative trop test

HOMOCYSTEINE

- Intermediate AA in conversion of methionine to cysteine
- Is an independent risk factor for the development of atherosclerotic vascular disease & venous thrombosis

USES

- Implicated directly in vascular injuries :

- Intimal thickening
- Disruption of elastic lamina
- Smooth muscle hypertrophy
- Platelet aggregation

- Screening recommended in patients with premature CV disease or unexplained DVT

- R_x – supplementation of folate, vit B_6 & B_{12}

GLOMERULA FILTRATION RATE

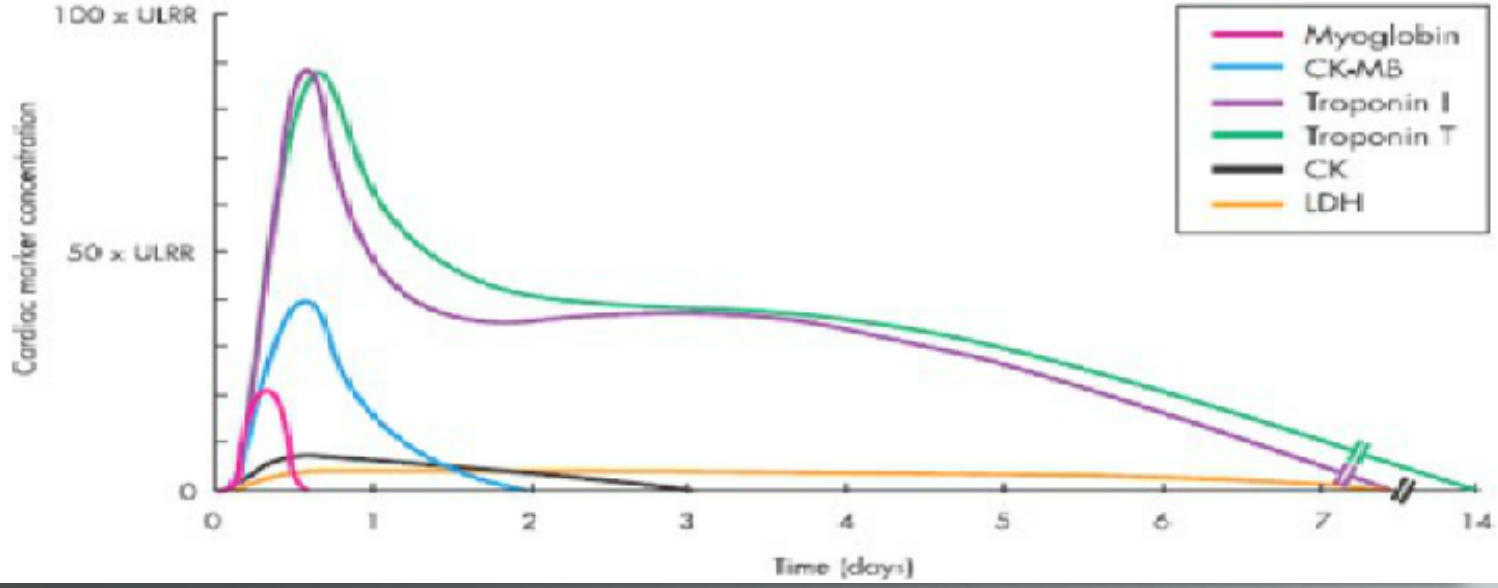
- CKD & CV risk are co-morbid conditions
- Creatinine clearance is inversely related to CV risk independent of co-morbid conditions
- Reduced GFR may be associated with :
- Increased inflammatory factors
- Abnormal lipoprotein levels
- Elevated plasma homocysteine
- Anemia
- Arterial stiffness
- Endothelial dysfunction

OTHERS

- Ischemia-modified albumin (IMA) – marker of ischemia
- Brain natriuretic peptide (BNP) – marker of CHF
- BNP increased in LVF & LVH

Properties of individual markers

Marker	Initial Rise	Peak	Persistence	Heart Specificity
CK	4 - 6 h	18 - 24 h	24 - 36 h	+
CK MB	4 - 6 h	16 - 20 h	18 - 30 h	++
Myoglobin	1 - 2 h	4 - 6 h	8 - 12 h	+
Troponin I	4 - 6 h	18 - 24 h	5 - 7 d	++++
Troponin T	3 - 5 h	18 - 24 h	5 - 7 d	++++



ELEVATED CARDIAC BIOMARKERS IN NON-ACS SITUATIONS

- Sepsis (SIRS)
- Hypovolemia
- Atrial fibrillation
- PE & Pulmonary hypertension
- HF acute & cronic
- Myocarditis & pericarditis
- Tachycardia
- Situations of prolonged myocyte ischemia
- Tachy/bradyarrhythmias
- Prolonged/profound hypotension

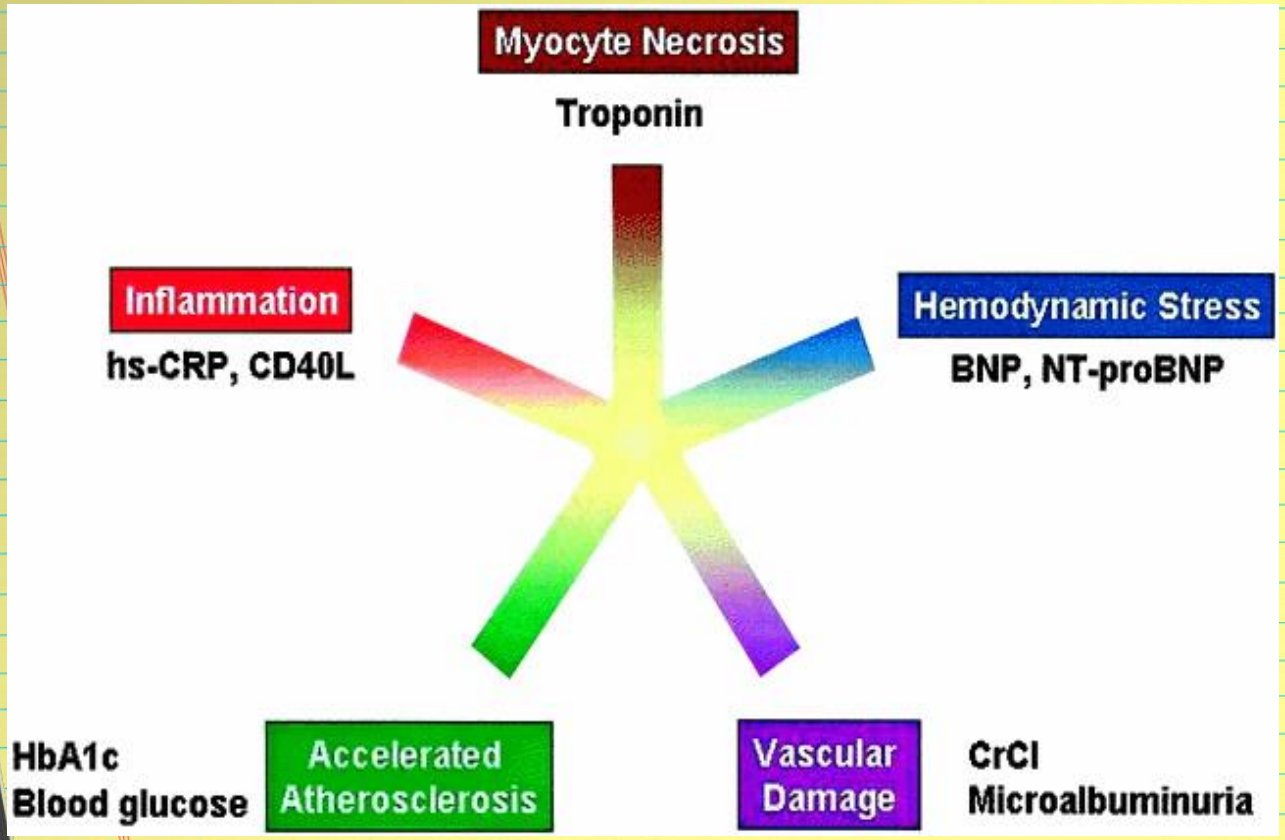
ELEVATED CARDIAC BIOMARKERS IN NON-ACS SITUATIONS

- CPR/Cardiac contusion
- Electrical Cardioversion/ICD firing
- Renal failure
- Apical Ballooning syndrome
- Chemotherapy, e.g. Adriamycin, Herceptin
- Toxins
- Cocaine
- Extreme exertion e.g. Marathons,
- LVH

The Future of Cardiac Biomarkers

- Many experts are advocating the move towards a *multimarker strategy* for the purposes of diagnosis, prognosis, and treatment design.
- As the pathophysiology of ACS is heterogeneous, so must be the diagnostic strategies.

A Multimarker Approach Should Focus on Multiple Mechanisms / Pathologies



Potential Components of a "Multimarker" Approach

Components	Examples
Biomarkers	
Markers of myocardial strain	Natriuretic peptides, osteoprotegerin, ST2
Markers of myocardial cell damage	Cardiac troponins (sensitive)
Markers of inflammation	C-reactive protein, interleukin-6, growth differentiation factor-15, myeloperoxidase, tumor necrosis factor-α
Markers of atherosclerosis	Lipoprotein (a), lipoprotein-associated phospholipase A_2, oxidized low-density lipoprotein
Renal markers	Cystatin C, kidney injury marker-1, neutrophil gelatinase-associated lipocalin, urinary albumin–creatinine ratio
Genetic markers	
Noninvasive measures	
Measures of subclinical atherosclerosis	Coronary artery calcification, carotid intima-media thickness, ankle-brachial index
Measures of endothelial function	Flow-mediated vasodilation of brachial artery
Measures of arterial stiffness	Pulse wave velocity, aorta augmentation index
Exercise parameters	Heart rate recovery, exercise capacity

Recommendation of ESC guidelines 2011 on biomarkers for diagnosis and prognostic assessment in ACS

Biomarkers for diagnosis and risk stratification in ACS

Prognosis

- BNP/NT-proBNP
- (hs)-CRP

Diagnosis

Inflammation or oxidative stress:

- MPO
- GDF-15
- LPAP-2A

Earlier ischemia markers:

- hFABP
- IMA
- Copeptin

"However, the incremental value—particularly over highly sensitive troponin tests—has not been evaluated, thereby presently precluding any recommendations for routine use"

ESC guidelines 2011

TAKE A HOME MASSAGE

- Cardiac biomarkers is just a LAB result>> please correlate it with the your patient clinical presentation.

- Use Multimarker Approach is best than single marker Approach.

THANK YOU