Markers to evaluate heart function

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Lab Tests to monitor risk factors for myocardial ischemic events

- Homocysteine
- LDL raise; HDL decrease;
- Cholesterol; Triglycerides;
- High sensitivity C-Reactive Protein;
- PAPP-A (pregnancy associated plasma protein-A);
- IMA (Ischemic Modified Albumin)

Diagnosis of Acute Myorcardial Infarct

Based on 2 out of 3 of WHO criteria *(Circulation, 1979)*

- Prolonged chest pain
  - "Silent infarct", Painless infarct
- ECG changes
  - Lacks sensitivity
- Serum enzyme concentrations
  - CK-MB lacks sensitivity in diagnosis of perioperative MI
  - Protein markers, e.g. troponins, myoglobin & others emerging in the 21st century

Ideal Marker to Detect AMI

- Rapid release into blood following myocardial injury
- High concentration in myocardium
- Absent in non-myocardial tissues
- High sensitivity & specificity
- Remain in blood several days to allow detection
- Blood levels correlate with extent of myocardial injury & prognosis
- Monitor the success of reperfusion after thrombolytic therapy

Early Diagnosis of MI in ER

- Expedite triage of patients in ER
  Appropriate use of beds in ER
- Timely management of thrombolytic therapy
- Missed diagnosis of AMI by ER physicians

Cardiac Markers of the 21Century

- MB isoenzymes
- CKMM isoforms
- CKMB isoforms
- Myoglobin
- Troponin I
- Troponin T
- Pro-B Natriuretic Peptide
- Ischemia modified albumin
- C-reactive protein

Myoglobin

- Oxygen binding protein of cardiac and skeletal muscle (MW=17,800 Da)
- Rapid release from infarcted area over some limited time, rapid transport to serum
- May rise significantly within 1-2 h of muscle cell damage and after onset of AMI
- Rapid renal clearance; return to normal level within 24 h

Events that are linked to an increase of Myoglobin

- Acute myocardial infarction

but also in:

- Open heart surgery
- Skeletal muscle damage, muscular dystrophy, inflammatory myopathies
- Renal failure, severe uremia
- Shock and trauma

Clinical Usefulness of Myoglobin

- Slow technology (RIA) in the past had limited extensive clinical use as a cardiac marker
- Rapid monitor of success of thrombolytic therapy
- Negative predictor of MI

however, keep in mind that:

- Due to poor specificity, raise in myoglobin levels do not always predict myocardial injury.

Myoglobin as Cardiac Marker

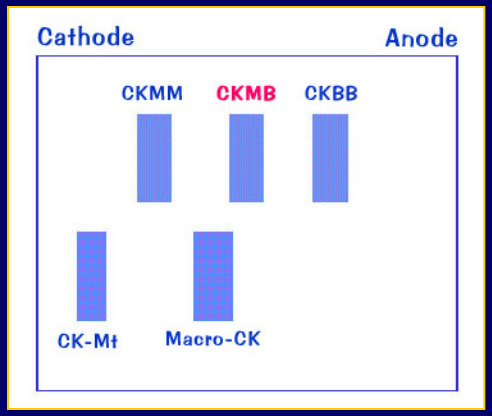
- Collect at least 2 samples within 2h for myoglobin determination
- Calculate slope of myoglobin release
- Use 20 ng/mL/h as cut-off point

Clinical Role of Myo in ED

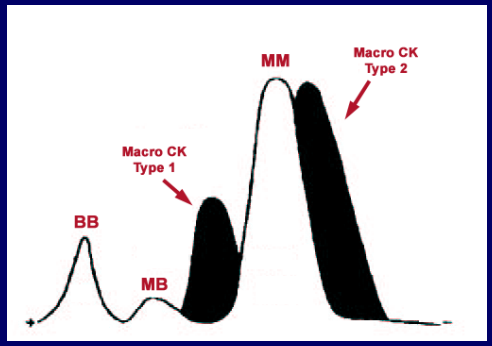
- Two Myo, instead of single Myo, is much more specific for detecting AMI in the first 2 h of ED admission.
- Renal failure is much less problematic when 20 ng/mL/h is used as cut-off.
- Because of rapid rise and rapid clearence, VERY EARLY and VERY LATE MI presenters will be missed.

CK Isoenzymes

- Isoenzymes
  - CK-3 (CK-MM) in skeletal muscle. 95% of the circulating CK
  - CK-2 (CK-MB). 5% of circulating CK
  - CK-1 (CK-BB). Absent under physiological conditions.



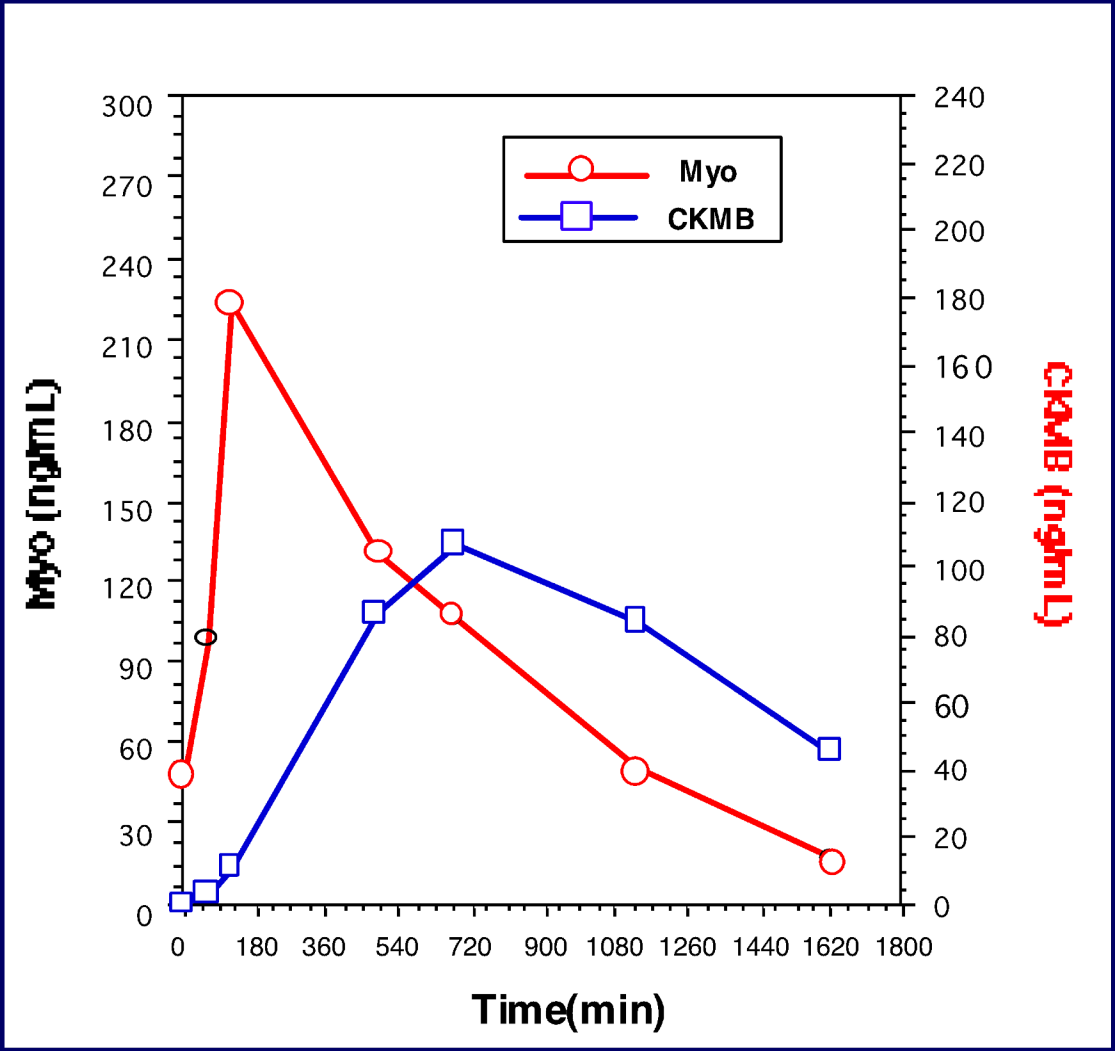
- Macro CKs
  - Type 1
    - Complex formed between CK-BB and immunoglobulin
  - Type 2
    - Mitochondria CK



MB Index

- MB Index = CK-MB x 100/CK
- Rationale for using MB Index
  - Using CKMB alone (RI <5.0 ng/mL) often yields False Positive results
  - Combined use with MB Index helps to rule-out patients with skeletal muscle injury
- What cut-off value for MB Index to use?

CKMB & Myoglobin in a Typical MI



CKMB Isoforms

MB = 18 U/L

MB2

MB
(U/L)

Look for ↑ MB2/MB1

MB = 5 U/L

RI

MB = 2 U/L

MB2

MB1

MB2

MB1

MB1

Baseline 4 h 12 h

MB2/MB1 = 1.0 3.5 3.2

Limitation of CK-MB

- False Positive incidents in perioperative patients without cardiac injury

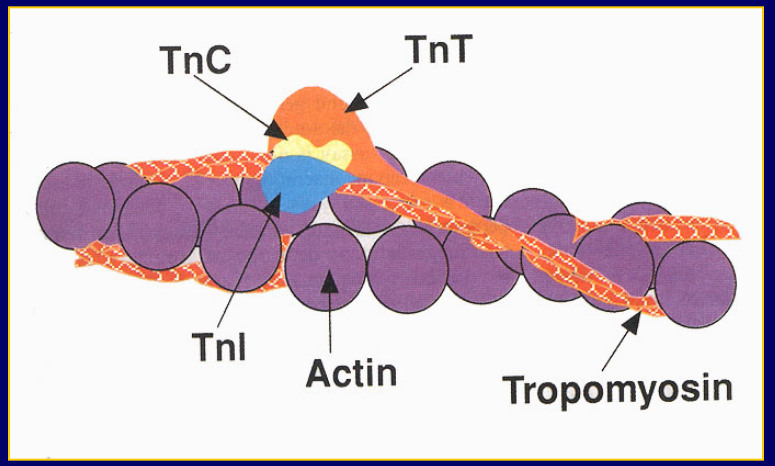
- False elevations in
  - Skeletal muscle injury
  - Marathon runners
  - Chronic renal failure
  - Hypothyroidism

- MI detection not timely enough for thrombolytic intervention. MB peaking takes >12h

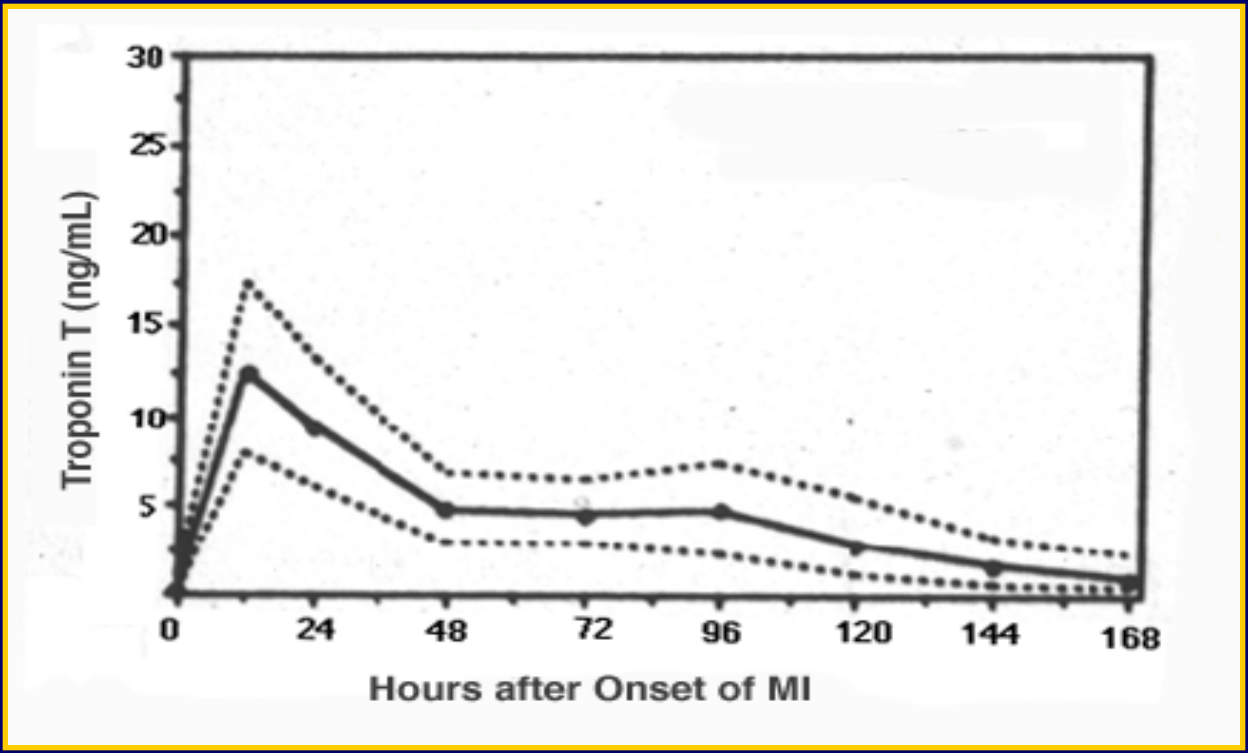
Troponins

- Regulatory proteins in striated muscle
- Responsible for calcium-modulated interaction
- Exist in a number of isoforms

- Cardiac specific forms immunologically separable:
  - Troponin T (TpnT)
  - Troponin I (TpnI)



Troponin Release Kinetics

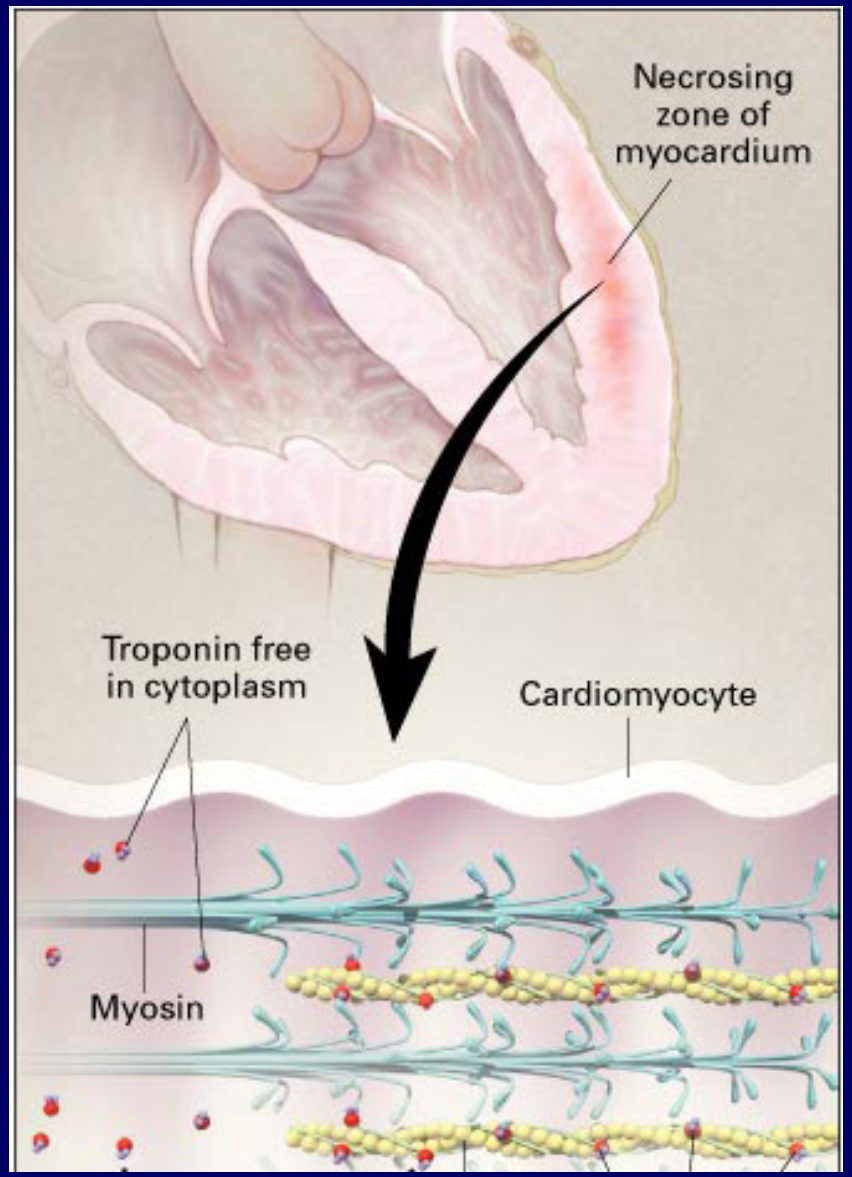


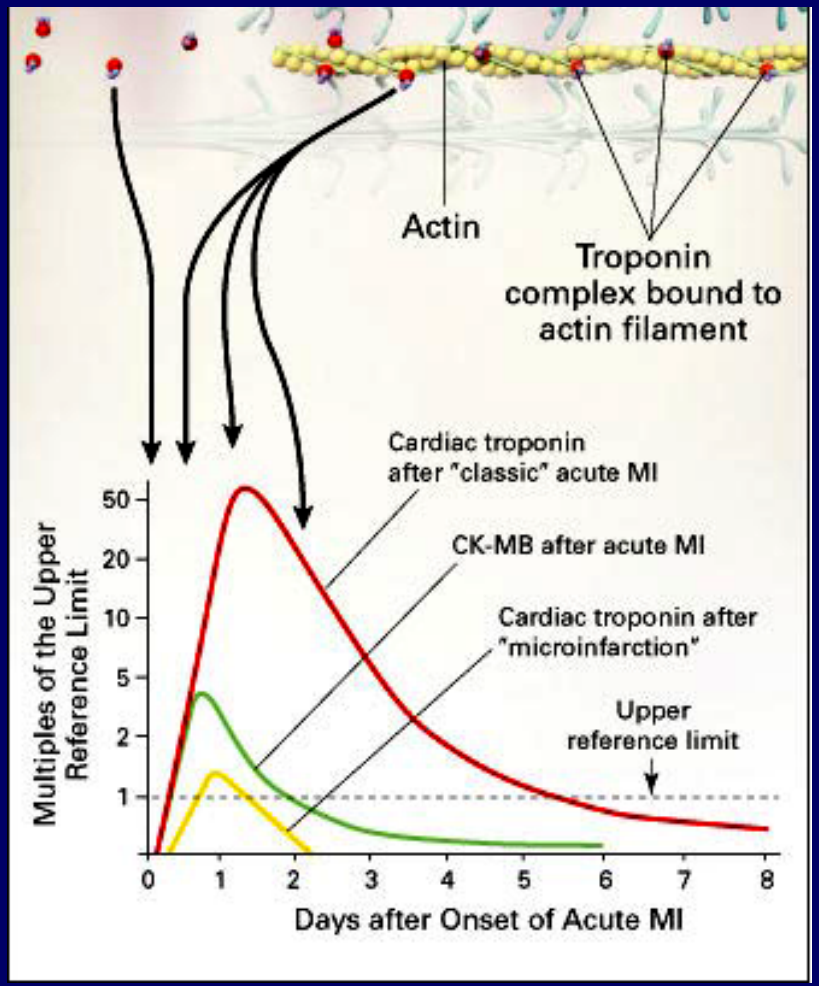
- Pattern of release in MI is BIPHASIC.
- Detectable in blood 4-12 h, similar to CKMB
- Peaks 12-38 h
- Remains elevated for 5-10 days

Cardiac Troponin I & T

- Cardiospecific. Immuno distinct from skeletal muscle isoform
- In cardiac muscles, Tn's tightly bind to contractile apparatus. Serum level normally low.
- "Cytosolic pool"
  - 6% Tpn-T and 3% Tpn-I
- Tpn-T assay available in Europe in early 90's. FDA approved first Tpn I assay in the USA in 1995.

Cardiac Troponin Release after MI



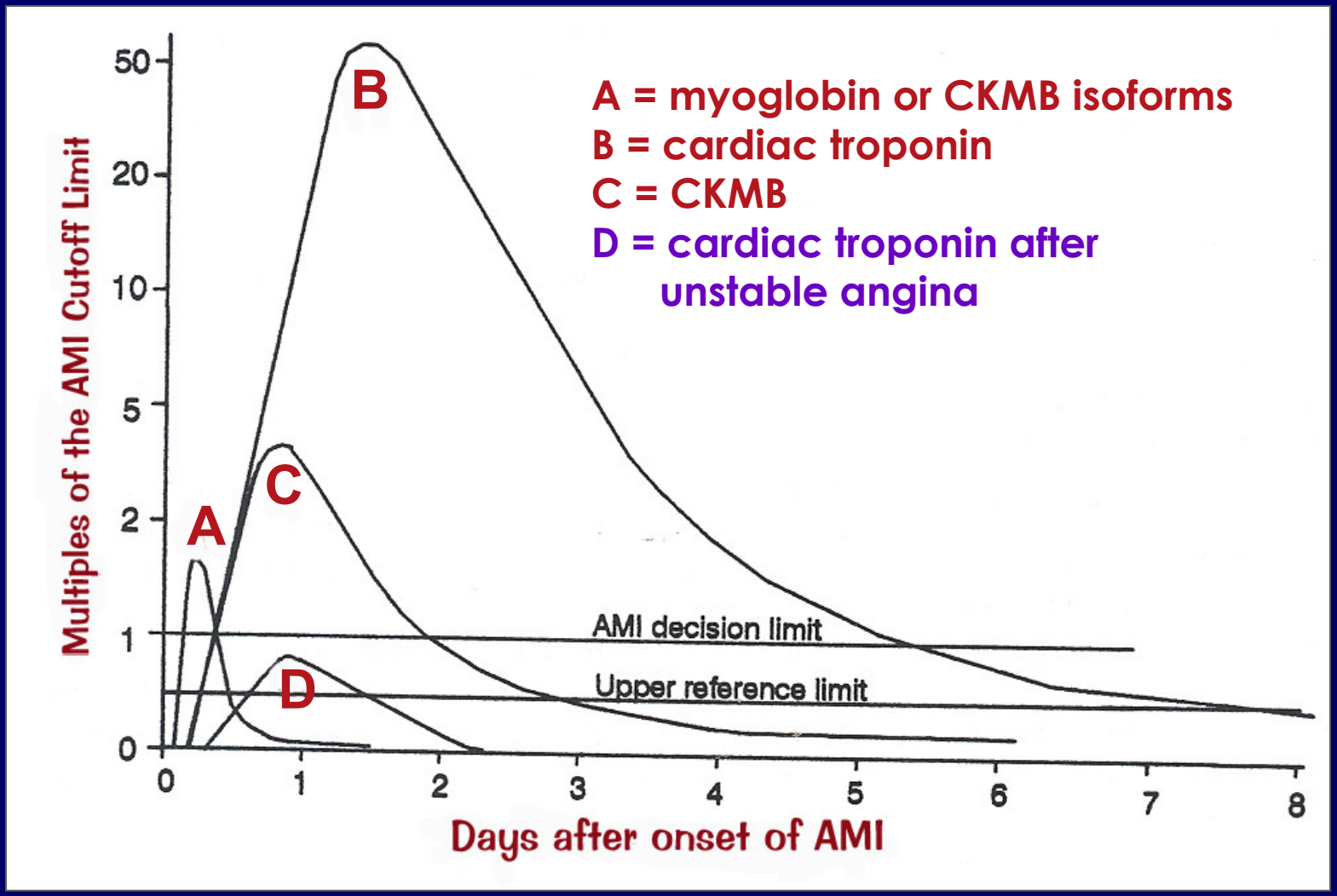


Defining Increased Troponin

- Tpn-T and -I are not detected in healthy persons
- Significant ↑Tpn reflects myocardial necrosis
- Detectable ↑Tpn but no ↑ CKMB may indicate microinfarction
- ↑Tpn identifies high-risk ACS patients for aggressive anti-thrombolytic therapy

- ACC/ESC defined ↑Tpn as a measurement above 99th percentile value of reference group
- To reduce false-positive outcomes, Critical Value of ≤10% at decision limit is recommended

Marker Responses to MI



Diagnosis of AMI in the Troponin Era

Based on ESC/ACC's redefinition of MI *(JACC, 2000)*

- **Typical rise and fall of Troponin or CKMB with one of the following:**
  - **Ischemic symptoms**
  - **Development of Q wave on ECG**
  - **ST-segment elevation/depression**
  - **Coronary artery intervention**
- **Pathologic (morphologic) findings of AMI**

Clinical Usefulness of TnI & TnT

- Risk stratification in patients with acute myocardial ischemia
- To enable aggressive intervention with angioplasty or thrombolytic therapy
- To allow triage of patients suspected of MI but without definitive clinical findings
- To allow patients with low risk for MI to be sent home

Prognostic values of TpnT & TpnI

- Studies have shown
  - A +ve TpnT result at presentation more prognostic info than CKMB.
  - +ve TpnI correlates with risk.
  - TpnT > TpnI providing prognostic info on 30-day mortality
- Conc in cytosolic pool
  - TpnT (7-8%) > TpnI (2.5%)
  - Earlier release of TpnT upon myocardial necrosis may explain higher TpnT +ve patients
  - TpnI not as sensitive to early minor necrosis due to smaller cytosolic compartment

TROPONIN I

I.Epidemiology

A.Sensitivity: 100% of Myocardial Infarctions

B.Specificity: Low (36% have Unstable Angina)

II.Advantages

A.More specific than Troponin T

B.Not falsely elevated in Chronic Renal Failure

III.Technique: ED Acute Coronary Syndrome evaluation

A.Obtain 2 Troponin values 6 hours apart

IV.Interpretation

A.Level >1.0 to 1.2 suggestive of Myocardial Infarction

B.Two negative values 6 hours apart

1.Predicts low likelihood of Acute Coronary Syndrome

TROPONIN T

I.Epidemiology

A.Sensitivity: 94% of Myocardial Infarctions

B.Specificity: Low (22% have Unstable Angina)

II.Advantages

A.Highly sensitive for detecting Myocardial Infarction

B.Level may also help to risk stratify afterward

C.Qualitative test run in 10 minutes

III.Disadvantage

A.Less specific than Troponin I

1.Elevated in Unstable Angina

2.Elevated in Chronic Renal Failure

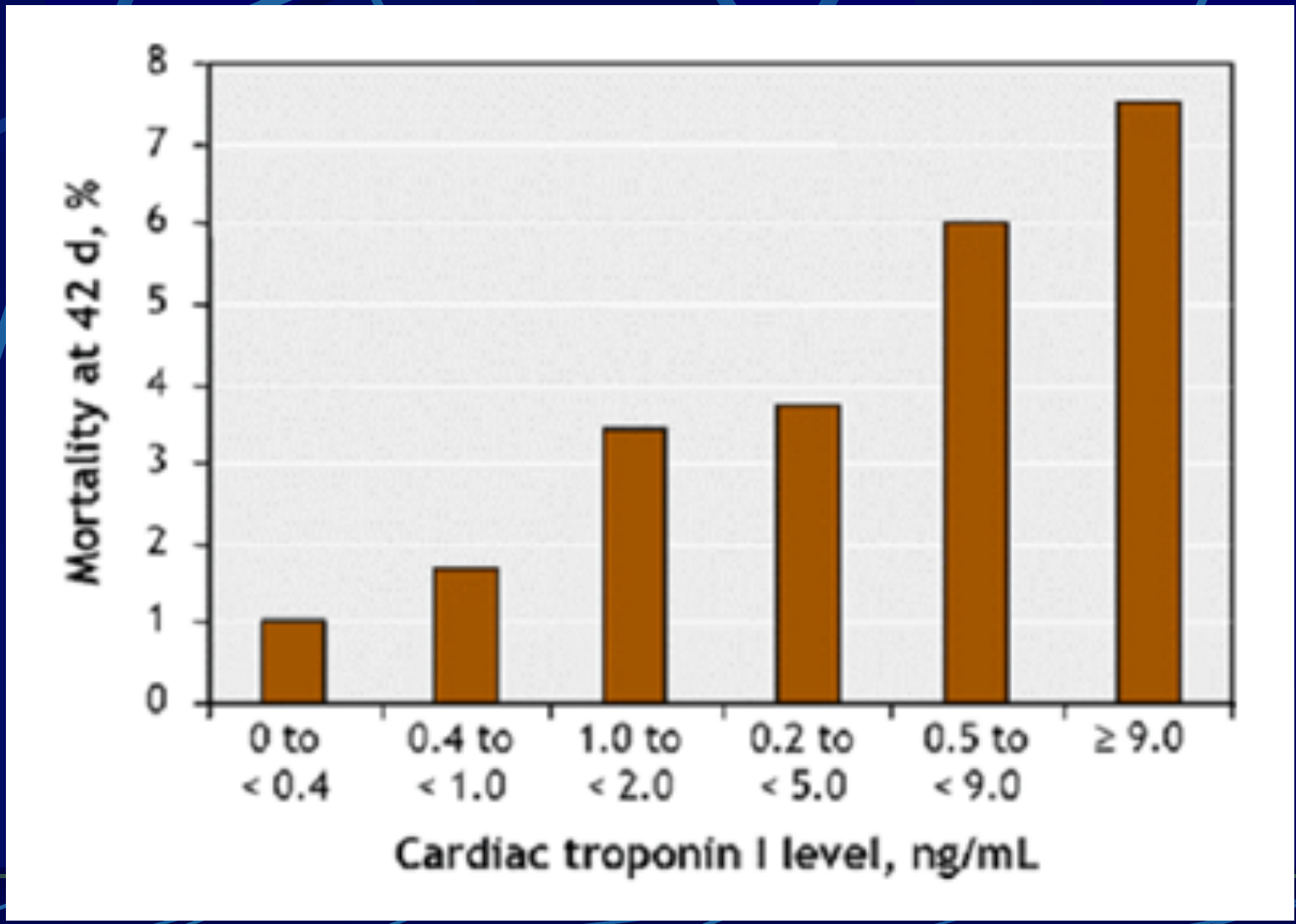
B.Levels stay elevated for days

1.Unable to time acute coronary event

IFCC & NACB Guidelines

- Early marker to be performed in ED
  - ↑ within 6 h, e.g. myoglobin. Good for r/o AMI
  - Rapid triage & thrombolytic therapy if onset is within 6-12 h
- Definitive marker
  - ↑6-12 h, sensitive & specific, e.g. TpnT, TpnI
- Decision limits
  - A low level suggestive of myocardial damage
  - A high level suggestive of AMI

Tpn after Cardiac Surgery



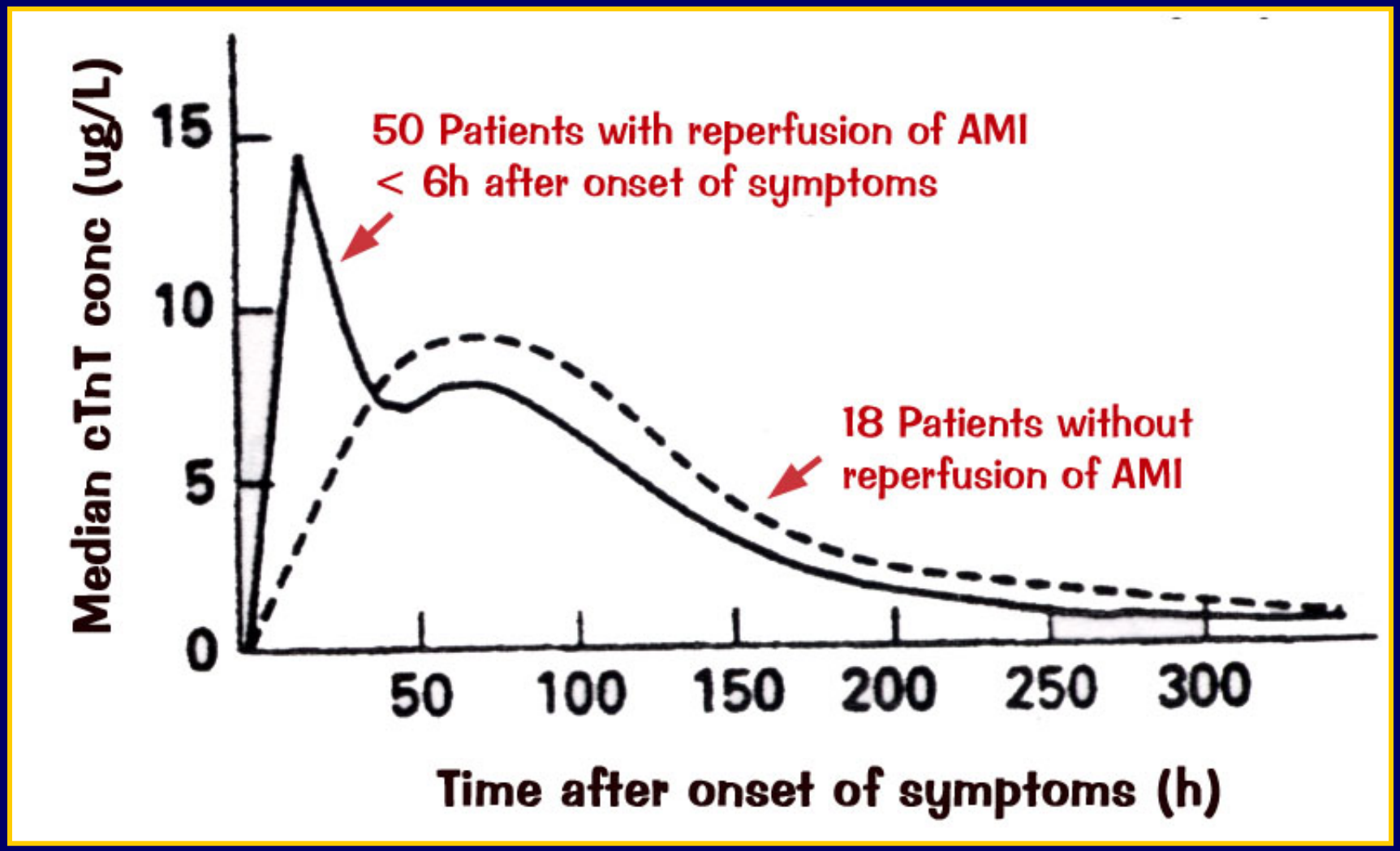
↑Tpns without Ischemic Heart Disease

Box 3: Conditions in which troponin levels may be elevated without overt ischemic heart disease

- Trauma (e.g., contusion, ablation, pacing, ICD firings, cardioversion, endomyocardial biopsy, cardiac surgery)
- Congestive heart failure, acute and chronic
- Aortic valve disease and hypertrophic obstructive cardiomyopathy with significant left ventricular hypertrophy
- Hypertension
- Hypotension, often with arrhythmias
- Noncardiac surgery without complications
- Renal failure
- Severe asthma
- Critical illness, especially diabetes, respiratory failure, hemolytic uremic syndrome
- Drug toxicity (e.g., adriamycin, 5-fluorouracil, herceptin, snake venoms)
- Hypothyroidism
- Coronary vasospasm, including apical ballooning syndrome
- Inflammatory disease (e.g., myocarditis, parvovirus B19 infection, Kawasaki disease, myocardial extension of bacterial endocarditis)
- Percutaneous coronary intervention without complications
- Pulmonary embolism, severe pulmonary hypertension
- Sepsis
- Burns, especially if total body surface area affected is > 30%
- Infiltrative diseases, including amyloidosis, hemochromatosis, sarcoidosis and scleroderma
- Acute neurologic diseases, including cerebrovascular accident and subarachnoid bleed
- Rhabdomyolysis with cardiac injury
- Transplant-related vasculopathy
- Vital exhaustion

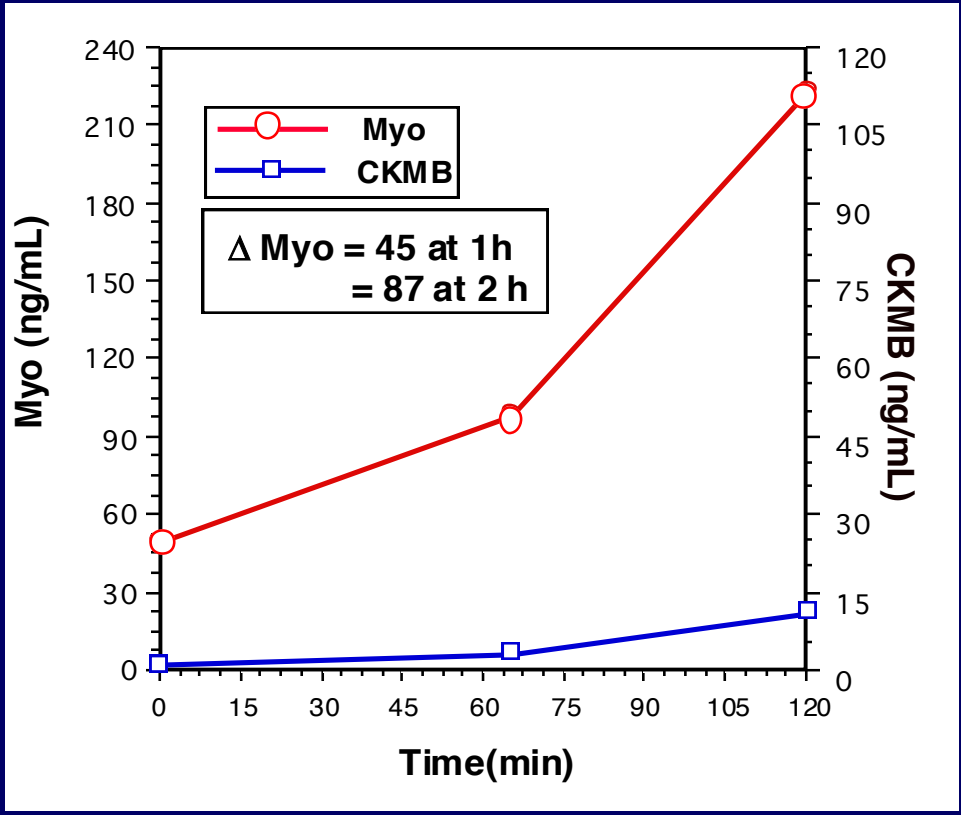
Note: ICD = implantable cardioverter defibrillator.

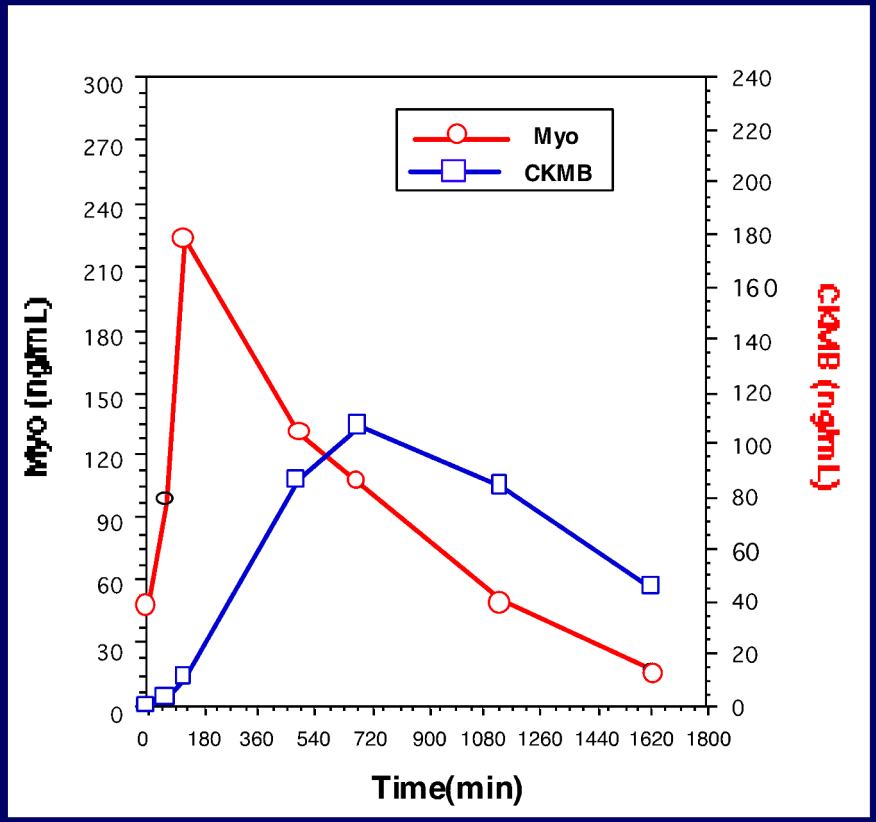
Antithrombolytic Therapy



Typical MI

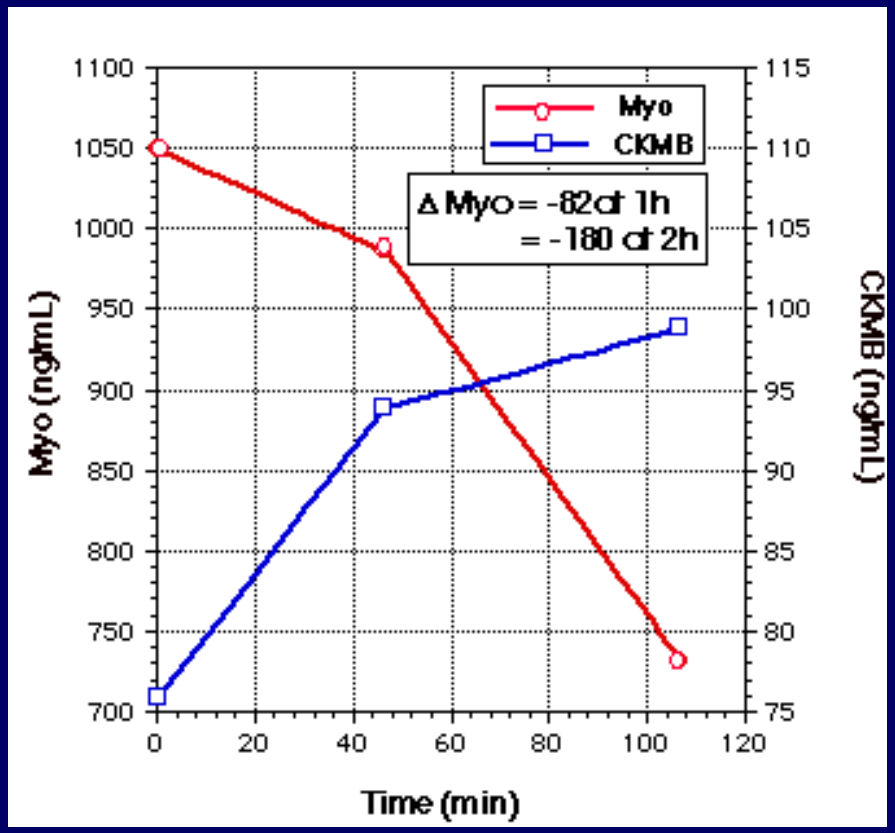
3 samples drawn within 2 h

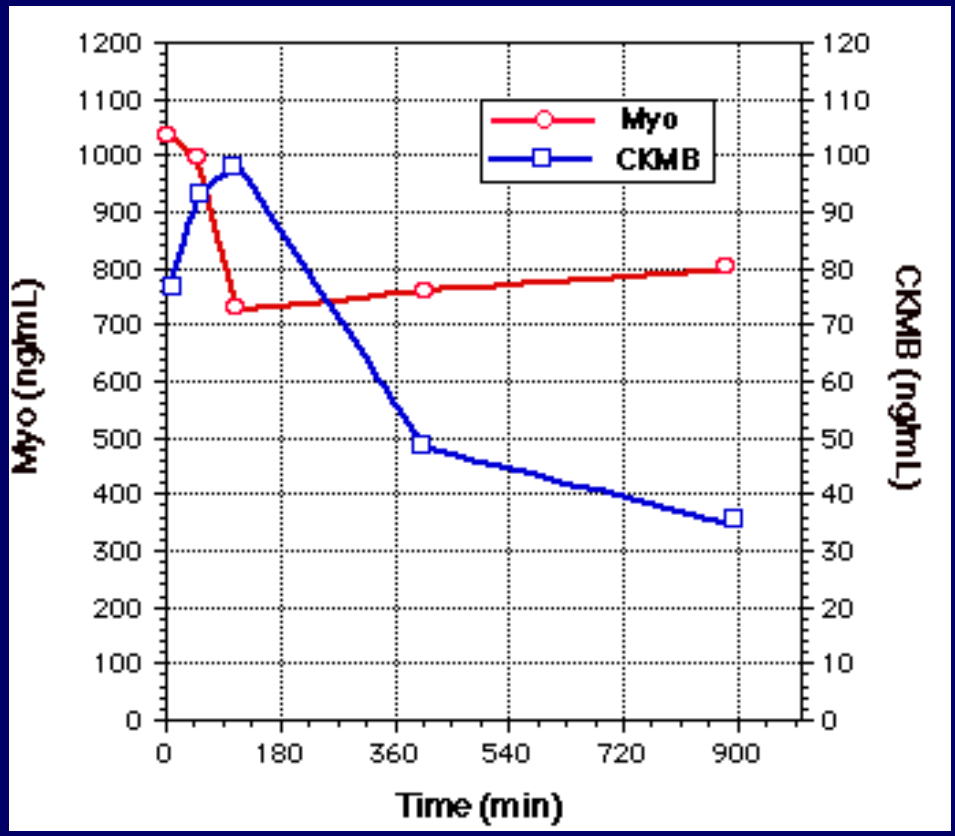




MI Concomitant with Renal Failure

3 samples drawn within 2h





Acute myocardial infarction and unstable angina

Ischemia-modified albumin (IMA)

is a novel marker of ischemia generated by the conformational modification in the N terminus of albumin, induced by the low pH environment during ischemia, and resulting in decreased transitional binding of cobalt to albumin .

(IMA) also rises rapidly after ischemia onset

Congestive Heart Failure

Brain natriuretic peptide and heart failure:

BNP & ANP are neuro-endocrine hormones, produced and secreted by the ventricles, that participate in fluid homeostasis by:

increase urine volume and urine sodium excretion

vascular smooth muscle relaxation

inhibition of the renin-angiotensin-aldosterone system and sympathetic nervous system

BNP is proportionately increased in conditions of high volume states, poor left ventricular function, and ventricular hypertrophy

elevated level of BNP was found to be highly sensitive (96%) and specific (96%) for the diagnosis of CHF.