Cardiac Markers

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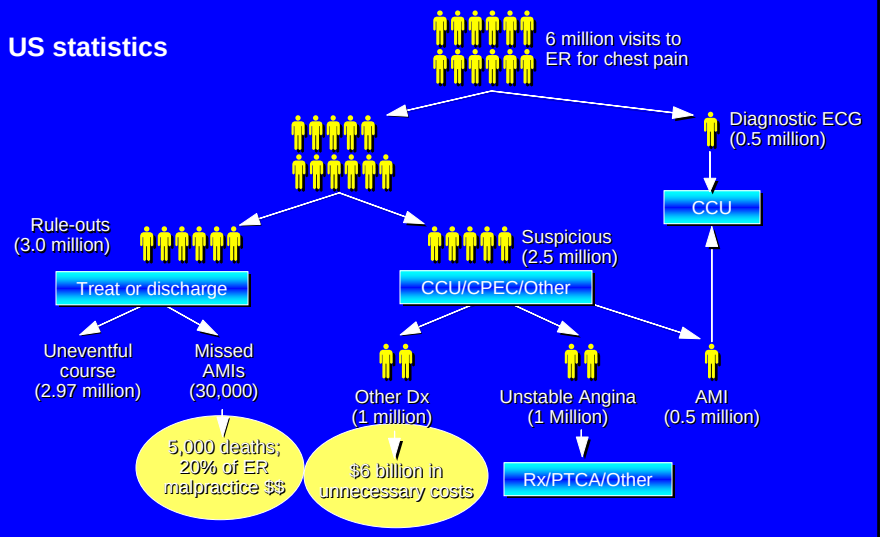
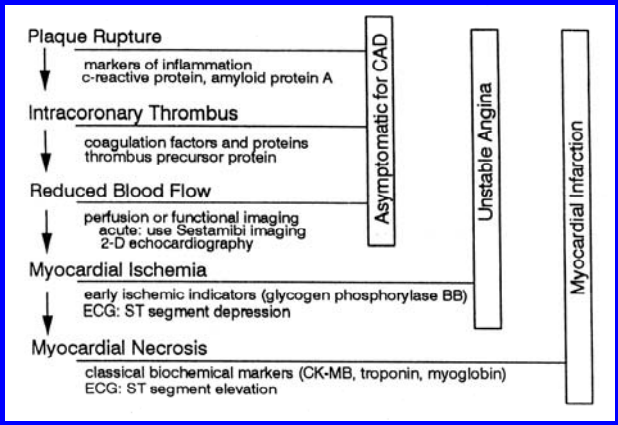
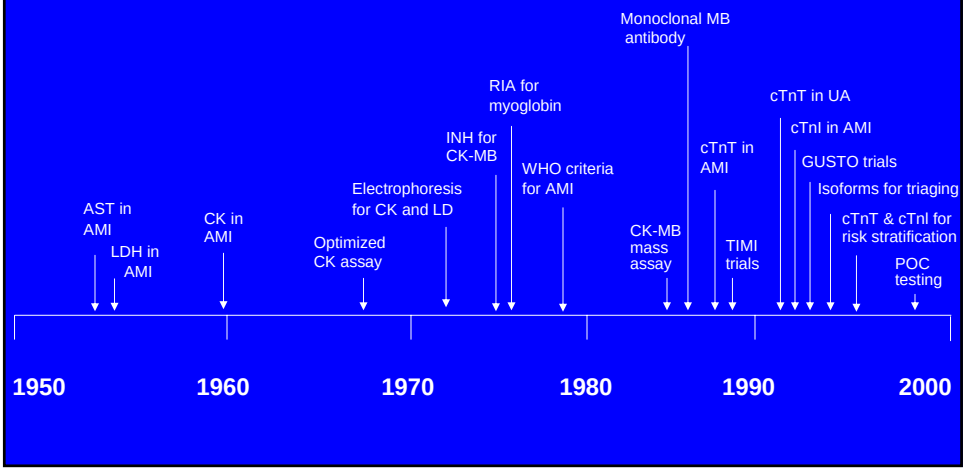
Current Chest Pain Triage Methods Result in Overadmissions and Missed MIs



PATHOPHYSIOLOGY OF ACUTE CORONARY SYNDROME



History of Cardiac Markers



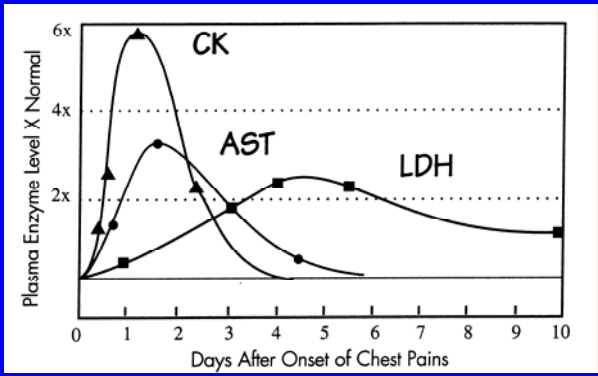
An Ideal Marker for Myocardial Injury Would Be

- Found in high concentrations in myocardium
- Released rapidly after the onset of pain
- Not be found in other tissues even in trace amounts or under pathological conditions
- Have a convenient diagnostic time window
- Reflect as much as possible the evaluation of myocardial damage

Serum Cardiac Markers of the Past

- Total CK Activity
- Aspartate Aminotransferase Activity
- Lactate Dehydrogenase Activity
- LD1/LD2 Ratio

CARDIAC MARKERS OF THE PAST

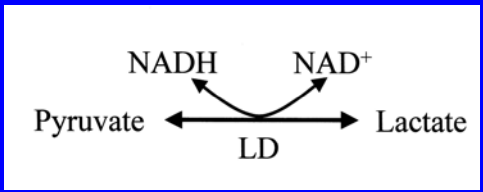


Aspartate Aminotransferase (AST)

Creatine Kinase (CK)

Lactate Dehydrogenase (LDH)

Lactate dehydrogenase (LD)



- **LD activity is measured by monitoring absorbance at X = 340 nm (NADH)**
- **Total LD activity has poor specificity**
- **LD has a molecular mass of 135 KDA and is a tetramer composed of heart and skeletal muscle subunits given rise to five isoenzymes**

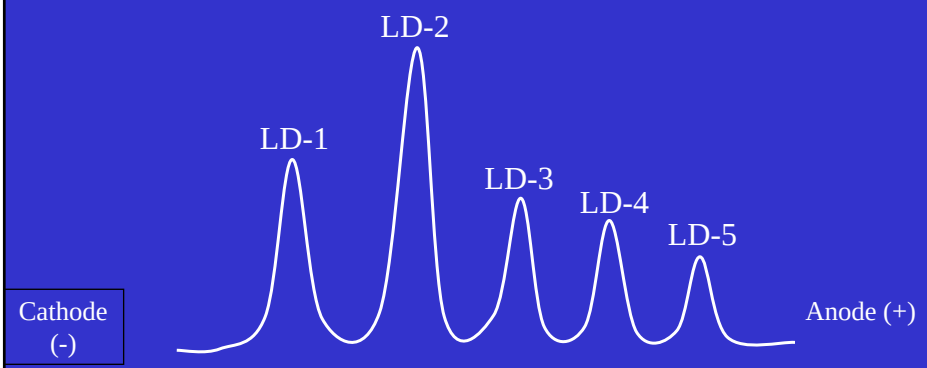
Distribution of LD Isoenzymes in Human Tissue and Serum

% Distribution of LD Isoenzynes

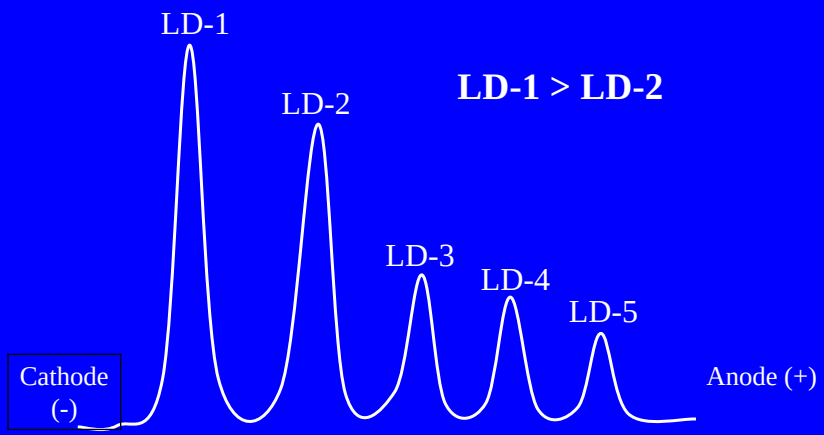
Tissue/Serum	LD1	LD2	LD3	LD4	LD5
Serum	29	38	0	7	6
Heart	52	29	16	2	1
Kidney-cortex	38	32	17	8	5
Erythrocyte	42	36	15	5	2
Brain	25	25	34	15	1
Lung	12	22	29	21	16
Spleen	6	11	35	28	20
Platelets	17	30	34	18	1
Leukocytes	8	12	50	18	12
Liver	2	2	3	12	80
Skeletal Muscle	1	4	8	9	78

LD isoenzyme electrophoresis (normal)

LD-2 > LD-1 > LD-3 > LD-4 > LD-5



LD isoenzyme electrophoresis (abnormal)



LD1/LD2

POST AMI

Increase	8-12 HRS
LD1/LD2 $\geq$ 1	48-72 HRS
Return to Normal	8-14 DAYS

Conditions Causing Flipped LD1/LD2 Without Acute Myocardial Infarction

- Hemolysis
- Megoblastic & Pernicious Anemia
- Renal Cortex Infarction
- Testicular Germ Cell Tumors
- Small Cell Lung Carcinoma
- Adenocarcinoma of the Ovary
- Acute Coronary Insufficiency (Unstable Angina)
- Exercise Induced Myocardial Ischemia
- Polymyositis
- Muscular Dystrophies
- Well Trained Athletes
- Rhabdomyolysis

Current Cardiac Markers

- CK-MB
- Myoglobin
- CKMB Isoforms
- Troponin I and T

Different Types of CK

CK: Dimer composed of 2 monomers: M (43,000 Da) and B (44,500 Da)---- > CK BB or CK MB orCK MM

Role:
Creatine + ATP <---> ADP + Phosphocreatine + Energy (muscular contraction)

CK BB = CK1 Increased in neurological diseases; prostatectomy; digestive cancers

CK MB = CK2 Increased with AMI

CK MM = CK3 Increased'in myopathy, hypothyroidy, polymyositis, rhabdomyolysis, traumatism, intensive exercise, AMI

Distribution Of CK & CK Isoenzymes in Various Tissues

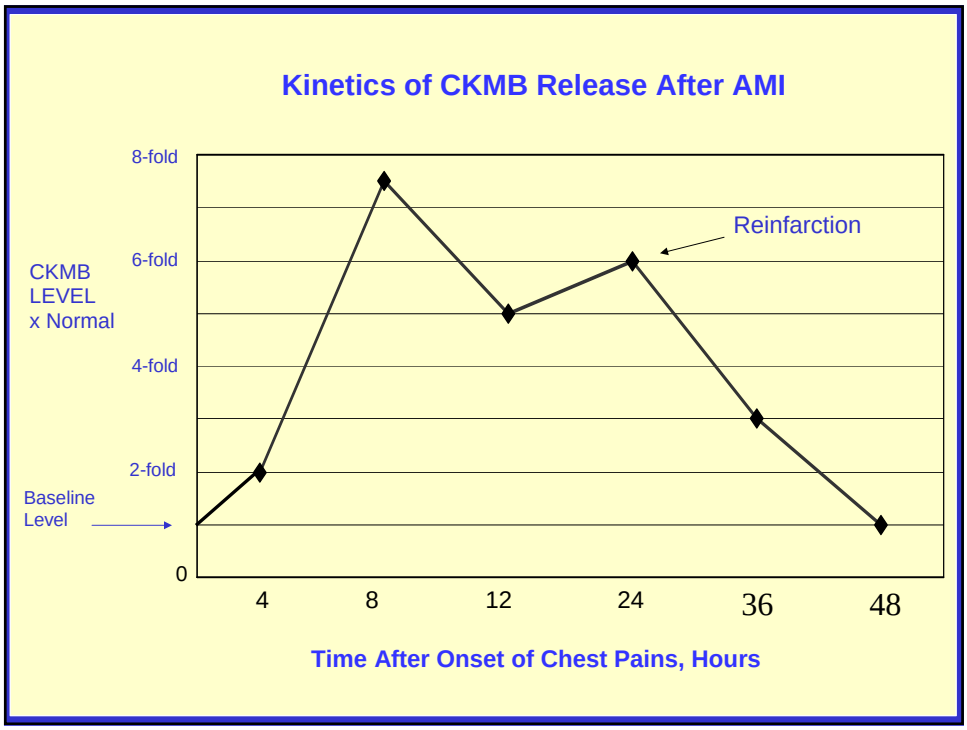
	Range of Total CK	Range of CK Isoenzymes (%)		
Tissue	U/gm tissue	MM	MB	BB
Skeletal Muscle	1080-3050	96-100	0-4	0
Heart Muscle	190-692	58-86	15-42	0-1
Brain	73-200	0	0	100
Bladder	162	0-2	0-6	92-100
Placenta	250	19	1	80
Colon	200	0-5	0-4	95-100
Ileum	175	0.3	0-4	93-100
Stomach	170	0-5	4	96
Diaphragm	140	96	4	22
Thyroid	32-34	7-11	0-6	90-96
Uterus	9-38	2-20	2-20	60-96
Kidney	10-50	0-13	0	87-100
Lung	13-24	0-39	0-7	58-100
Prostate	8-9	4-40	3-4	56-93

CKMB

AFTER AMI

Increase 4-6 Hours
Peak 10-24 Hours
Return to Normal 48-72 Hours

Draw blood on admission,4, 8, 16 and 24hr.



DIAGNOSTIC PERFORMANCE OF CKMB In AMI

	Sensitivity CKMB	Specificity CKMB
Admission	31	94
2 Hr	68	92
4 Hr	80	91
6 Hr	96	94

Limitations of CKMB in AMI

Elevated CKMB Levels can be observed in:

- Skeletal Muscle Involvement
- Duchenne Muscular Dystrophy
- Polymyositis
- Alcohol Myopathy
- Thermal or Electrical Burn Patients
- Carcinomas
- Colon, Lung, Prostate, Endometrial
- Atypical CK Isoenzymes and CKBB

CKMB IN AMI

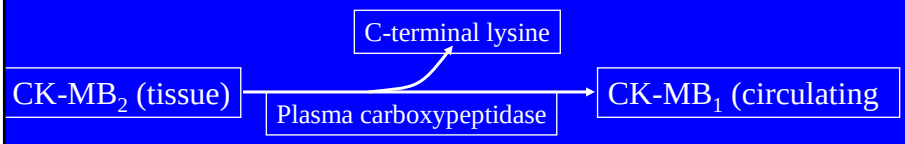
Advantages:

- Detects AMI 4-6 Hours After Chest Pain
- Methodology is Rapid and Automated
- Turnaround Time <60 Minutes

Disadvantages:

- Not Cardiac Specific

CK isoforms



- C-terminal lysine is removed from the M subunit--therefore, there are three isoforms of CK-3 (MM)
- $t_{½}$: CK-MB_1 > CK-MB_2
- Ratio of CK-MB_2 to CK-MB_1 exceeds 1.5 within six hours of the onset of symptoms
- Only method currently available is electrophoresis

Protocol for Early Detection of AMI

Draw Blood at 0, 1, 2, 3 hours

Measure CKMB Isoforms or Myoglobin

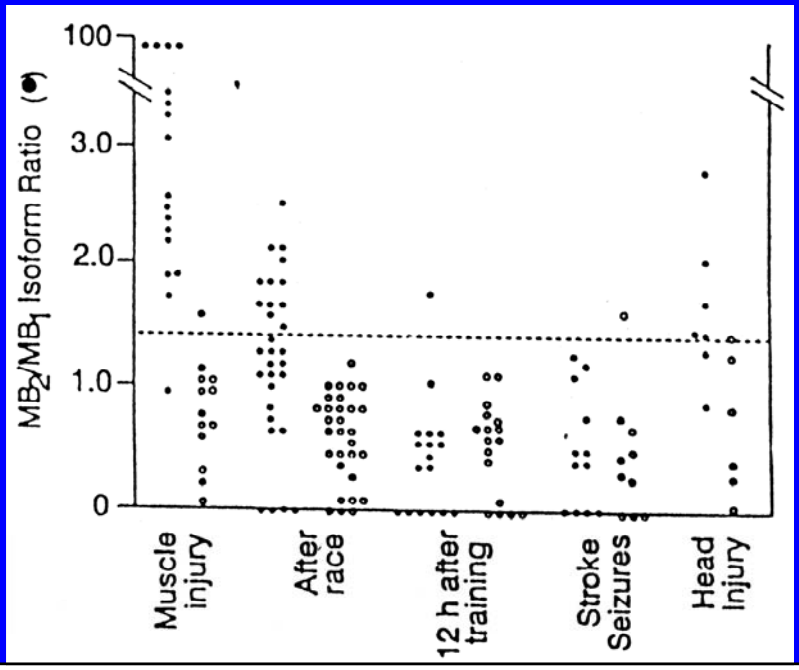
Re: *Puleo & Roberts*
New Engl. J. Med, 1 Sept 1994

- **1110 patients who came in Emergency Care Units for chest pain**
- **By using a ratio CKMB2ICKMBI > or = 1.5, as well as the CKMB2 value (0.5-1 UIL) in the 6 first hours after the onset of chest pain**

CKMB Isoforms and CKMB

Sensitivity , %

Time after onset, hr	CKMB Isoforms	CKMB
4	56	23
6	96	48



CK Isoforms in AMI

Advantages:

- Early detection of AMI with CKMB Isoforms

Disadvantages:

- Not Cardiac Specific
- Elevated in acute skeletal muscle trauma and in serum of marathon runners

Methodology Limitations

- Labor Intensive
- May not be able to detect small changes in CKMB Isoforms
- Requires careful interpretation of CK patterns
- Results not available in a timely fashion

Myoglobin

Definition:

- Oxygen-binding protein
- MW=17,800 kd
- Cytoplasmic
- Heart and Skeletal Muscle Tissue

Myoglobin

Present in Cardiac and Skeletal Muscle

Molecular Mass 17,800

Post AMI		Myoglobin	CKMB
Increase	Hrs	2-4	4-6
Peak	Hrs	5-9	10-24
Return to Normal	Hrs	24-36	36-76

Serum Myoglobin Levels in Various Conditions

Increased In:

- AMI
- Open heart surgery
- Exhaustive exercise
- Skeletal muscle damage
- Progressive Muscular Dystrophy
- Shock
- Renal Failure
- Following IM injection

Remains Normal:

- Chest pain without AMI
- CHF without AMI
- Cardiac catherization
- Moderate exercise

Myoglobin in AMI

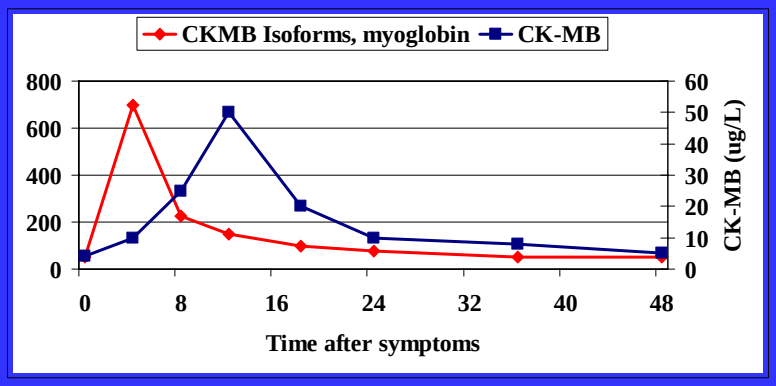
Advantages:

- Early Indicator of AMI
- Methodology - Automated
- Results Available in <60 Minutes

Disadvantages:

- Not Cardiac Specific
- Elevated in Trauma
- Skeletal Muscle Damage
- Exercise
- Impaired Renal Function

Temporal changes in CK-MB Isoforms, myoglobin and CK-MB



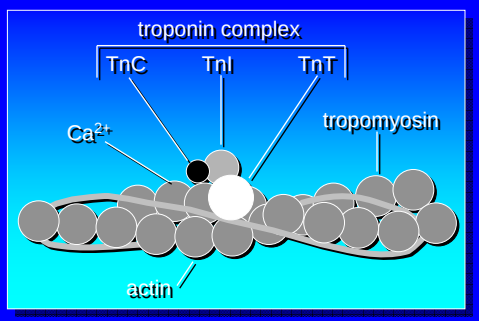
DIAGNOSTIC PERFORMANCE OF SERUM CARDIAC MARKERS In AMI

	Sensitivity			Specificity		
	CKMB	CKMB Isoforms	Myo	CKMB	CKMB Isoforms	Myo
0-2 Hr	7	19	22	93	100	92
2-4 Hr	12	32	27	95	93	80
4-6 Hr	73	85	81	96	95	70
6-8 Hr	90	95	95	95	90	50

Clin Chem,1996,42,1454-9.

Troponin Characteristics

- **Troponin C (18 kd)**
- Calcium-binding subunit
- No cardiac specificity
- **Troponin I (26.5 kd)**
- Actomyosin-ATP-inhibiting subunit
- Cardiac-specific form
- **Troponin T (39 kd)**
- Anchors troponin complex to theTropomyosin strand



The troponin complex consists of three different proteins (TnC, TnI, and TnT) that regulate the calcium-mediated contractile process of striated muscle.

Tissue specificity of Troponin subunits

- Troponin C is the same in all muscle tissue
- Troponins I and T have cardiac-specific forms, cTnI and cTnT
- Circulating concentrations of cTnI and cTnT are very low
- cTnI and cTnT remain elevated for several days
- Hence, Troponins would seem to have better specificity than CK-MB, *and* the long-term sensitivity of LD-1

Troponin I and T

Cardiac Specific Marker

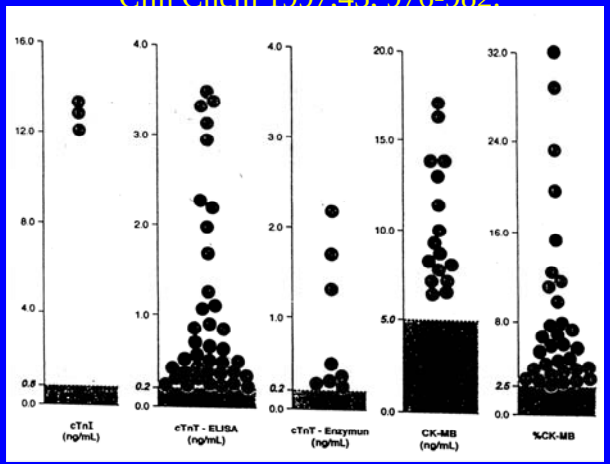
Post AMI		Troponin I	Troponin T	CKMB
Increase	Hrs	4-6	3-6	4-6
Peak	Hrs	14-24	10-24	10-24
Return to Normal	Days	5-7	6-10	2-3

Specificity of cTnl, CK-MB Mass & Myoglobin In Noninfarct Patients with Chronic Renal Failure or Severe Polytrauma

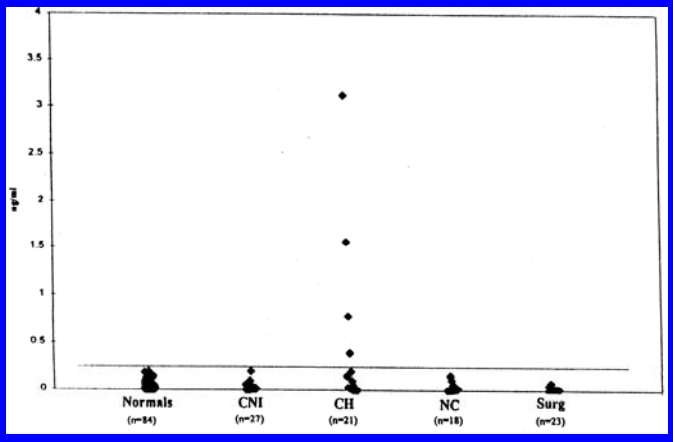
Pathology & Markers	No. (%) of Positive Sera	Specificity %
Severe Polytrauma (24 Sera)		
CK-MB mass	14(58)	42
Myoglobin	21(88)	12
cTnl	0 (0)	100
Chronic Renal Failure (49 Sera)		
CK-MB mass	4 (8)	92
Myoglobin	43(88)	12
cTnl	0 (0)	100

SERUM BIOCHEMICAL MARKERS OF 24 CHRONIC DIALYSIS PATIENTS WITHOUT ACUTE ISCHEMIC HEART DISEASE

Clin Chem 1997 43, 976-982.



Frequency Distribution of Cardiac Troponin I (cTnI) In Normals, Cardiac Non-Ischaemic (CNI), Congestive Heart Failure (CHF), Chest Pain of Non-Cardiac Origin (NC), And Surgical Trauma Patients (Surg)
Clin Biochem,1997,30,479-490.



Diagnostic Performance of Troponin I and Troponin T for AMI

	Sensitivity %		Specificity %	
	Troponin I	Troponin T	Troponin I	Troponin T
Admission	6	15	100	97
1 hr	25	38	100	96
2 hr	70	74	100	93
6 hr	96	97	99	93
12-24 hr	96	99	99	93

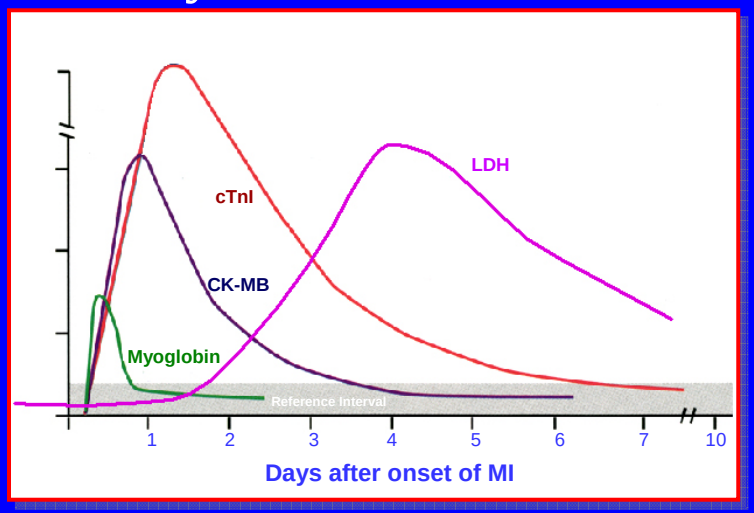
Troponin I, CKMB & Myoglobin

192 Patients With Chest Pain
59 Had An AMI

Clin Chem 45, 199-205, 1999

	Troponin I	CKMB	Myoglobin
		Sensitivity %	
<6 hr	65	78	75
6-24 hrs	72-93	78-80	73-75
		Specificity %	
<6 hr	100	91	74
6-24 hrs	94-97	82-86	68-82

Release of Cardiac Markers in Myocardial Infarction



Point-of-Care Testing For Cardiac Markers in the Emergency Department

- Solid Phase Chromatographic Immunoassay
- Quantitative and Qualitative Detection of CKMB, Myoglobin, Troponin I or T
- Whole Blood
- Assay Time-15-20 Minutes

Point-of-Care Troponin I & Troponin T

Hamm et.al., N Engl J Med 1997, 337,1648-83

773 Patients

47 AMI Patients

TnT positive-94%
TnI positive-100%
CK-MB positive- 91%

Unstable Angina Patients
TnT positive-22%
TnI positive-36%
CK-MB positive-5%

Use of Biochemical Markers for Detecting Myocardial Necrosis

- Myocardial Infarction redefined by joint European Society of Cardiology/American College of Cardiology (ESC/ACC) in 2000
- Recommendations
  - Tn – at least 1 value > cutoff in first 24 hrs
  - CK-MB – 2 successive samples > cutoff or 1 sample 2x cutoff
  - CK, AST, LDH – not recommended
- Testing Protocol
  - On admission, 6 – 9 hrs, and 12 – 24 hrs

JACC, 2000; 36:959-69