Cardiac Markers

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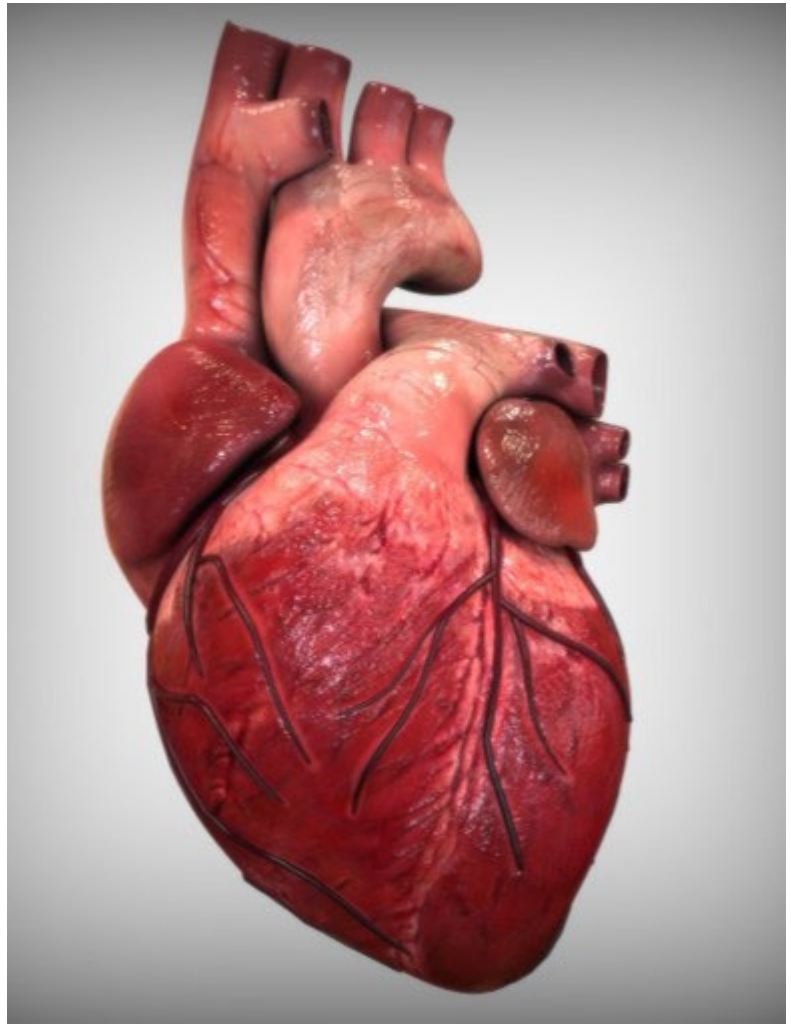


Objectives

Compare and contrast the specificity and sensitivity of commonly used cardiac markers.

Correlate laboratory results with cardiac conditions, including myocardial infarction.

Interpret cardiac function laboratory results given patient data.

Key Terms to Know

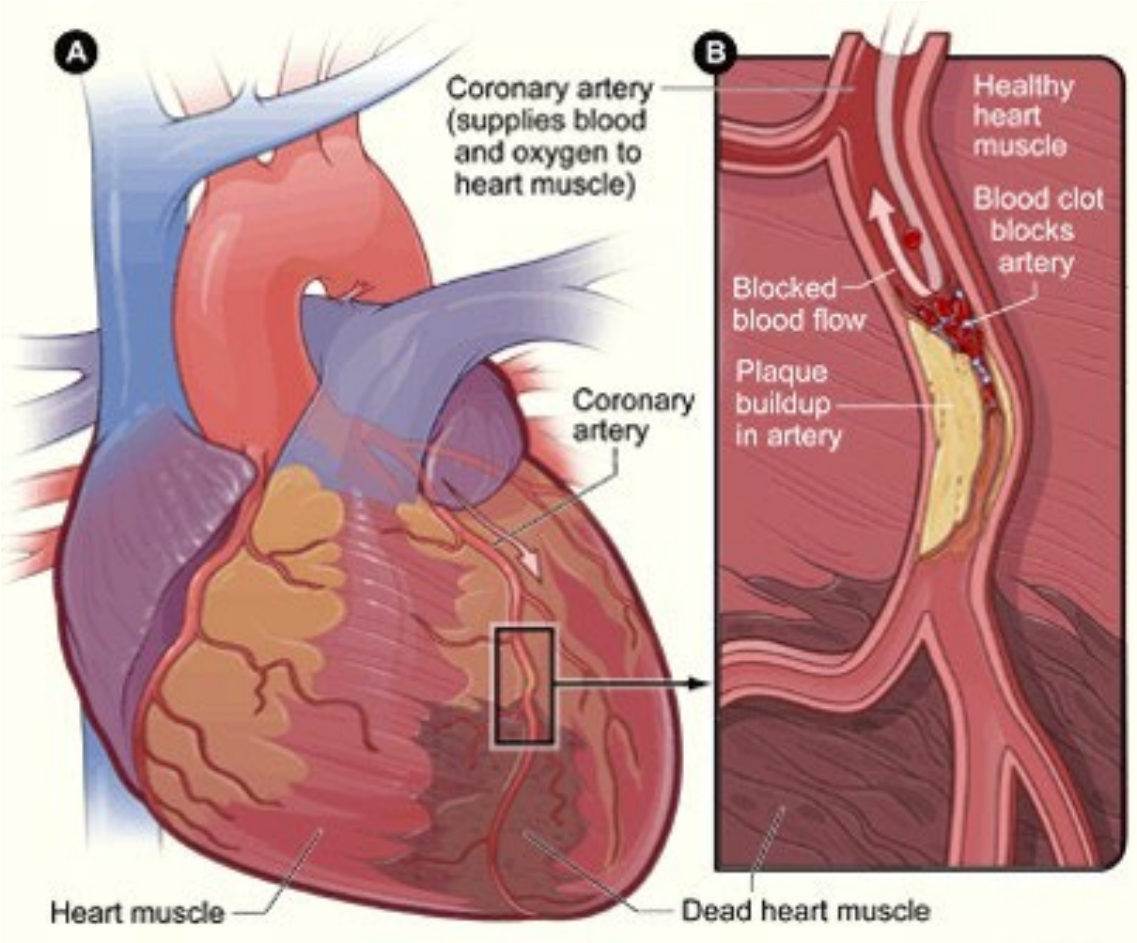
Atherosclerosis – buildup of plaque in the arteries, leading to narrowed blood vessels and reduced blood flow; can lead to

↓

Ischemia – lack of blood supply (and thus oxygen supply) to tissue; can lead to

↓

Myocardial infarction (MI) – death of heart muscle tissue; commonly referred to as heart attack

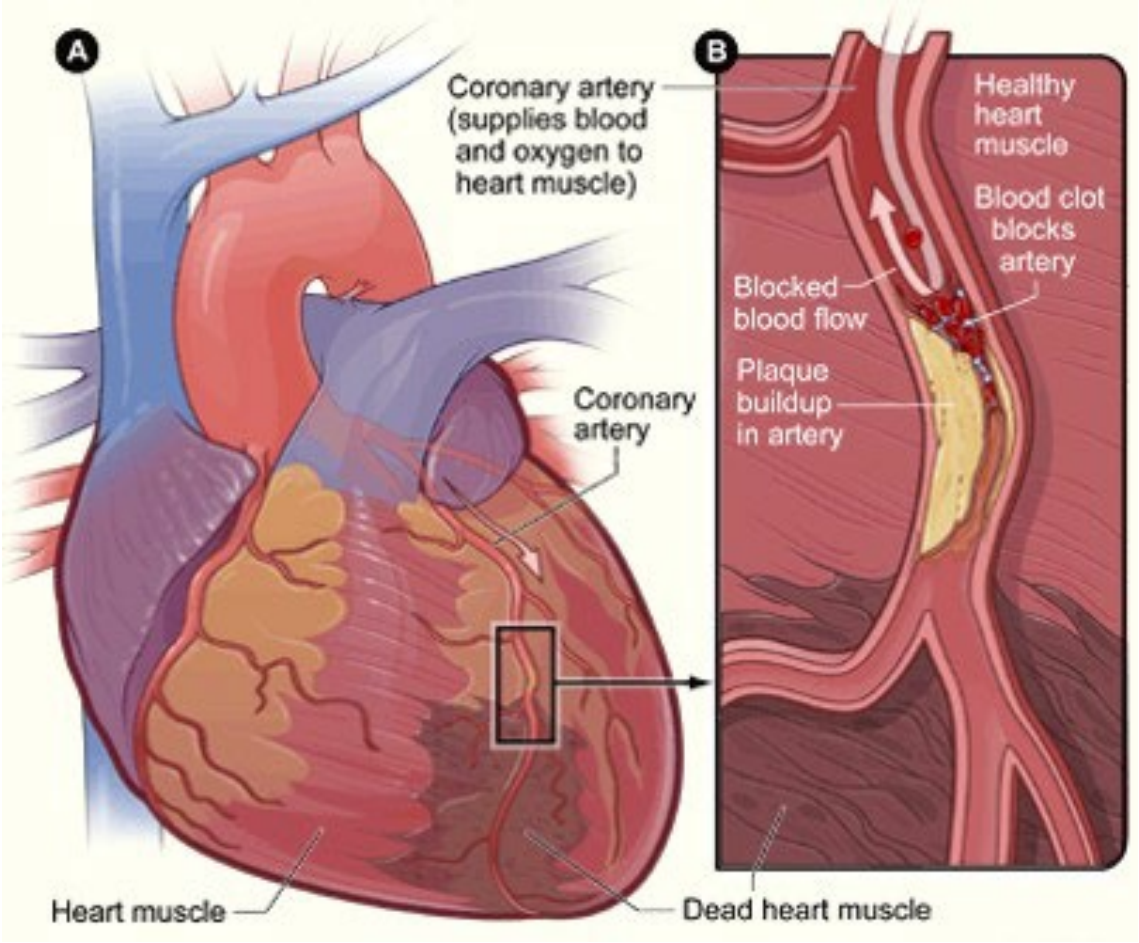


Cardiovascular Disease (CVD)

4 major types:

- Coronary heart disease (CHD)
- Cerebrovascular disease
- Peripheral arterial disease (PAD)
- Aortic atherosclerotic disease

In all cases, atherosclerosis is factor (just a matter of where)



Types of Cardiovascular Disease (CVD)

- Coronary heart disease (CHD)
  - Manifests as chest pain, **myocardial infarction** (heart attack), and **heart failure**
- Cerebrovascular disease
  - Blood supply is cut off to the brain
  - Manifests as stroke or transient ischemic attack (TIA)
- Peripheral arterial disease (PAD)
  - Manifests by blockage in the arteries to the extremities, usually the legs
- Aortic atherosclerotic disease
  - Manifests as aneurysms (abnormal widening of an artery) or dissection

Patient comes into ER with chest pain…

Critical to differentiate cardiac from non-cardiac causes of chest pain (i.e. heartburn or esophageal reflux)

Initially evaluated by:

- Physical examination
- ECG or EKG
- Chest x-ray
- **Laboratory cardiac markers**

Markers of Cardiac Damage

Underlying principle → cell death releases intracellular proteins and enzymes from the myocardium into the circulation

<u>Older</u> cardiac markers (enzymes)

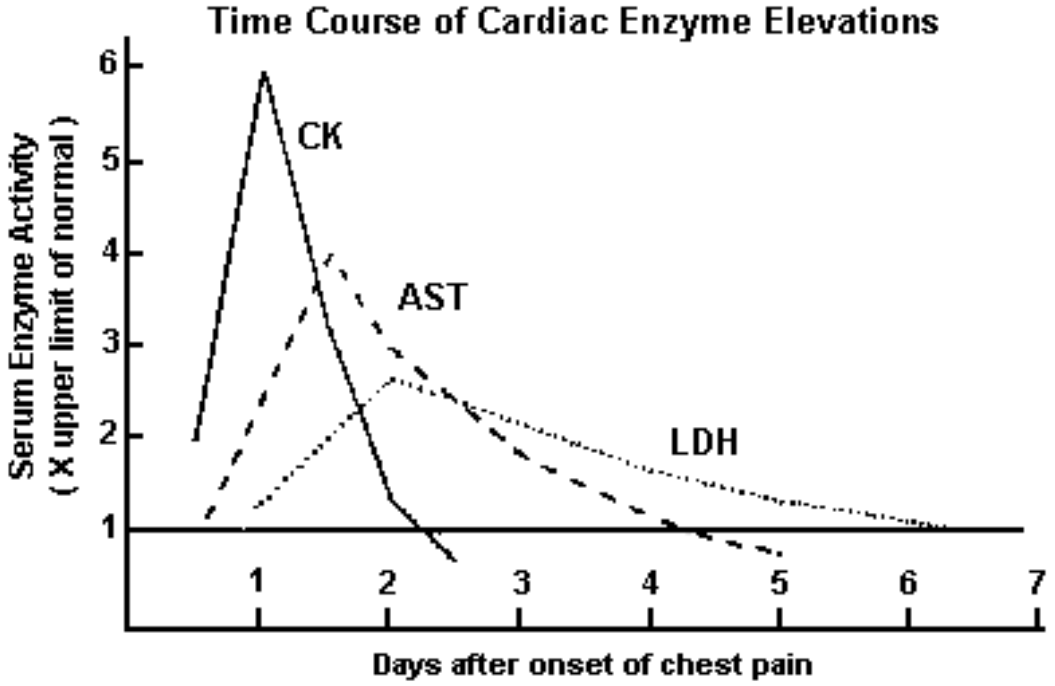
CK, AST, LDH (non-specific)

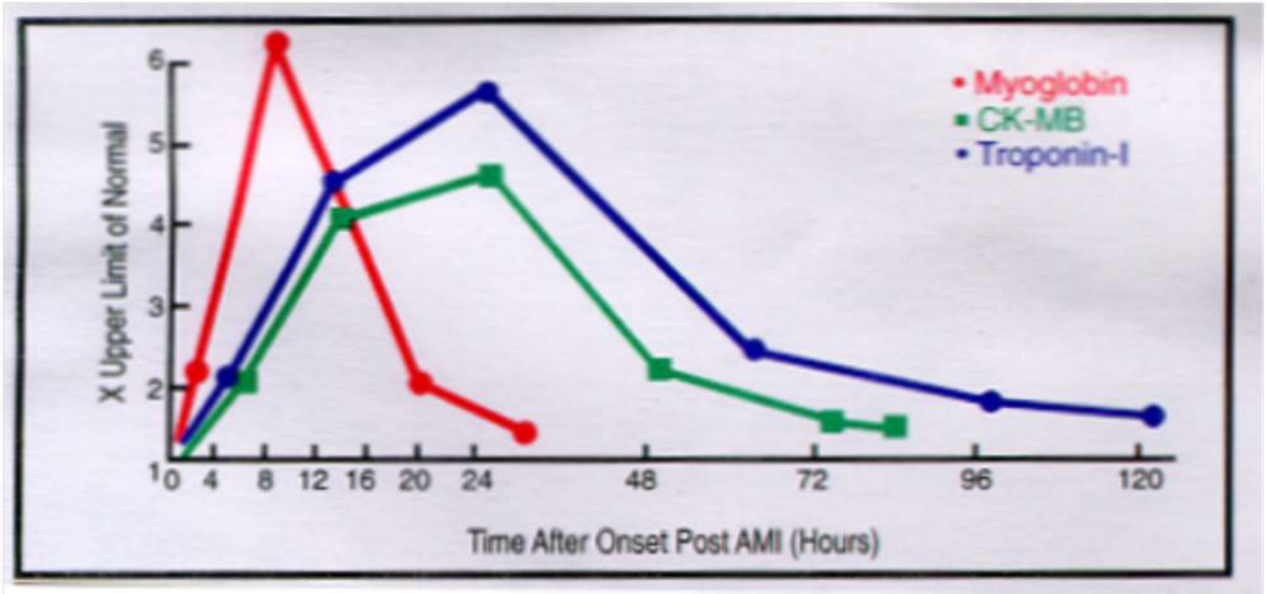
<u>Newer</u> cardiac markers

CK-MB

Myoglobin

Troponin T or I

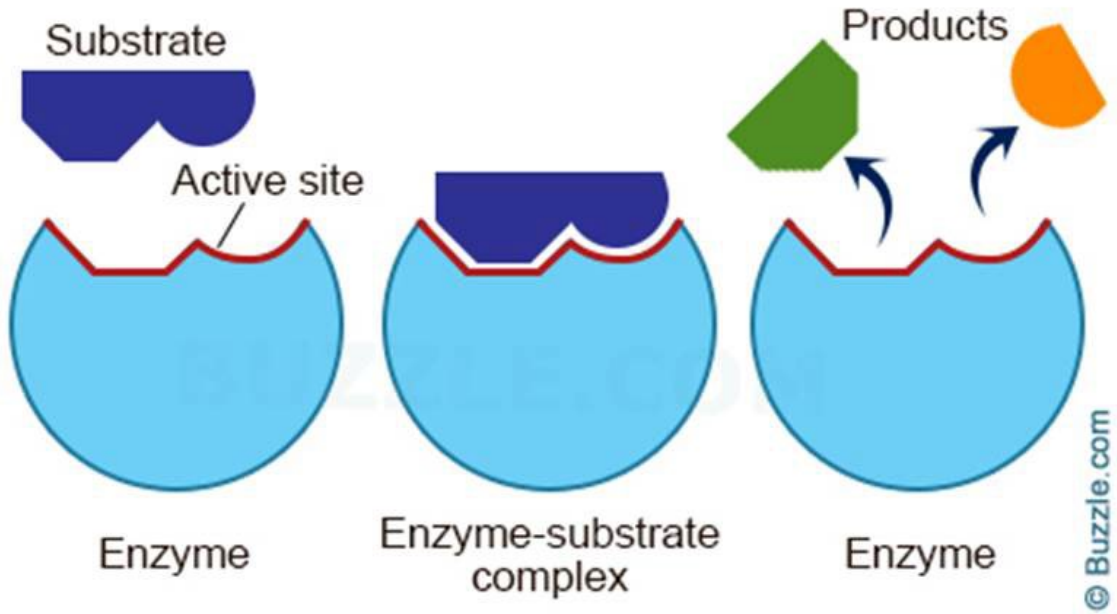




Enzymes

Mostly proteins that catalyze reactions without being consumed or altered in composition

- Found in body tissues and appear in plasma following cellular damage
- Some are naturally found in plasma (e.g. thrombin)



Enzyme	Tissue/Organ
ALT	Liver
ALP	Liver, bone
Amylase	Pancreas
AST	Heart, liver, skeletal muscle
CK	Heart, muscle
GGT	Liver
Lactate Dehydrogenase	Heart, liver, RBCs

Most enzymes have no physiological function in blood. They have been released from tissues.

Isoenzymes

Different forms of an enzyme that catalyze the same reaction

Can be separated by electrophoresis or some physical property

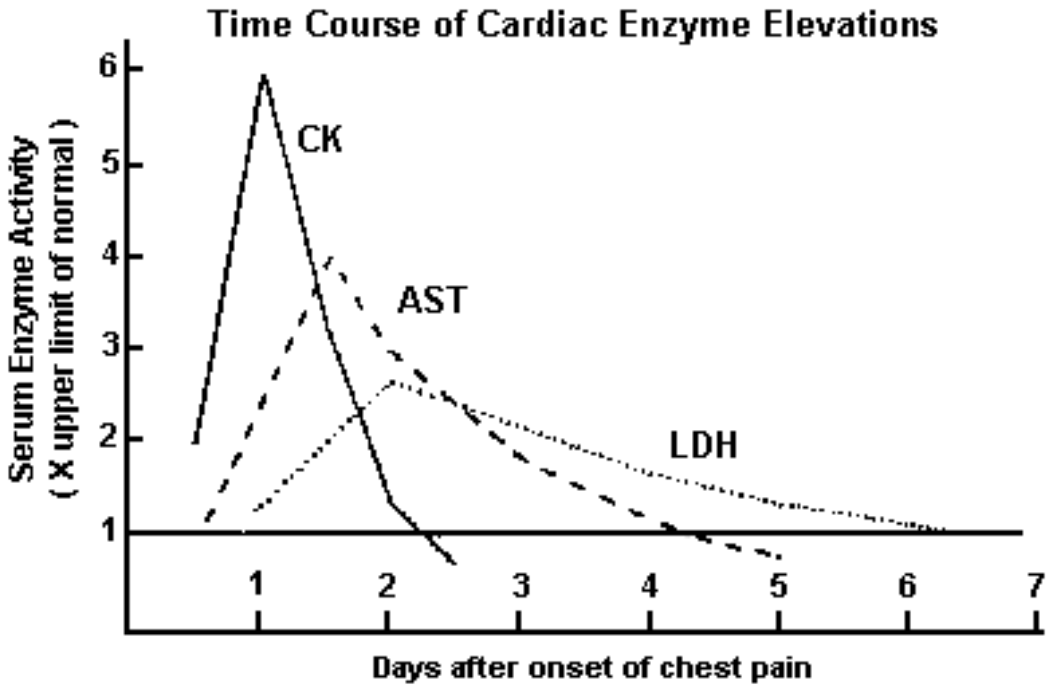
Isoenzyme assays can be performed to improve specificity

Creatine Kinase (CK)

Found in nearly all cells in the body (enzyme involved in ATP energy metabolism)

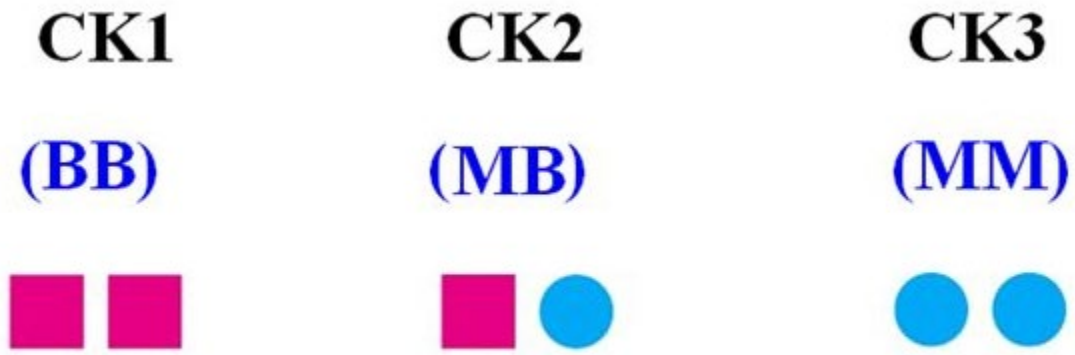
In patients with AMI, CK levels reach peak levels by 24 hours, and return back to normal within 2-3 days

An elevation of CK, AST, and LDH was used as the primary enzymatic detection of AMI for many years



Creatine Kinase Isoenzymes

CK isoenzymes are dimers composed of combinations of M and B subunits



CK-BB = CK1

CK-MB = CK2 (most cardiac spec.)

CK-MM = CK3

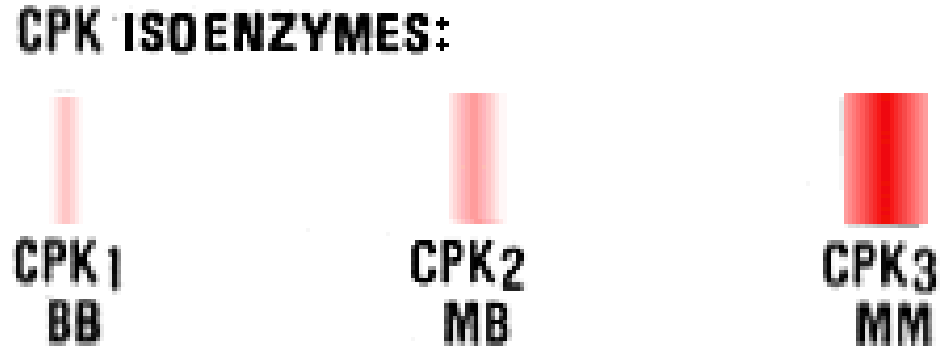
Clinically Relevant Isoenzymes

CK (Creatine kinase)-

CK-1 CK-BB

CK-2 CK-MB - most clinically relevant

CK-3 CK-MM



Separation: electrophoresis; immunoassay

Elevated levels of CK-MB ≥ 6% of total CK
is indicative of myocardial infarction

Isoenzyme	Subunit Composition	Primary Tissue Source	Clinical Significance
CK-BB	B + B	Brain, smooth muscle	↑ with brain injury, neurosurgery, malginancy
CK-MB	M + B	Cardiac muscle (some in skeletal)	↑ with myocardial injury used as a **cardiac marker**
CK-MM	M + M	Skeletal muscle (also in cardiac)	↑ with skeletal muscle injury, trauma, rhabdomyolysis

CK-MB (CK-2)

- Former “gold standard” for diagnosis of myocardial infarction

- CK-MB levels elevate rapidly post-MI (3-6 hours), peaks at 12-24 hours and returns to baseline after 2-3 days

↓

- Can only be used within a short window of time after a suspected MI

<u>Normal Range</u>: <6% of total CK (varies by method)

Aspartate aminotransferase (AST)

- An enzyme found in liver, heart, muscle, and kidneys
- Can be used as marker for tissue damage
- Elevated AST can indicate myocardial infarction, but it’s not heart specific
- More clinically significant for liver injury (hepatitis or liver disease)

Lactate Dehydrogenase (LD, LDH)

– tetramer composed of different combinations of H (heart) or M (muscle) subunits

LD-1 (HHHH)

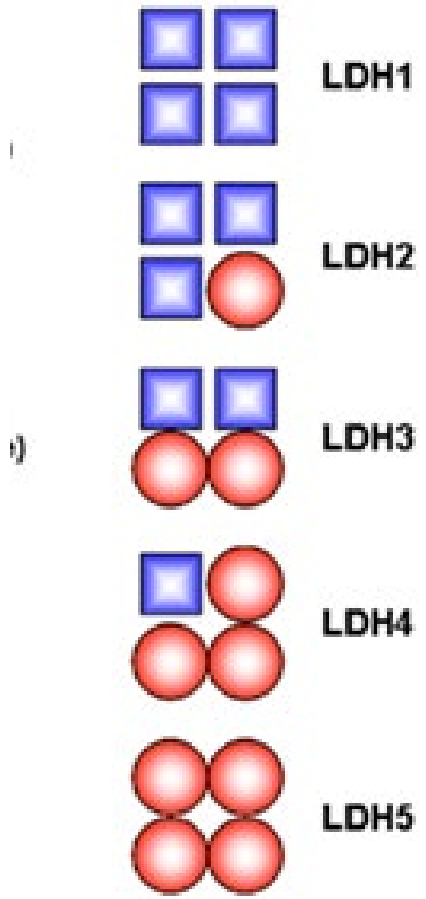
LD-2 (HHHM)

LD-3 (HHMM)

LD-4 (HMMM)

LD-5 (MMMM)

Normally LD-2 > LD-1 in blood

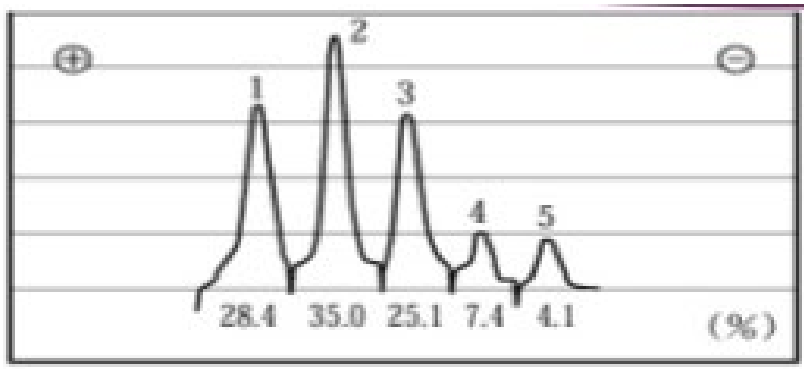


LD isoenzymes

LD-1 (HHHH)	**Heart and RBCs**	**Elevated in MI**
LD-2	Also in heart and RBCs	Normally higher than LD-1
LD-3	Lung, spleen, pancreas	May be ↑ with pulmonary embolism
LD-4	Liver	↑ in liver disease
LD-5 (MMMM)	Skeletal muscle	↑ in skeletal muscle injury

“Flipped” LD pattern **LD-1 > LD-2** **suggests MI**

Normally, LD-2 > LD-1



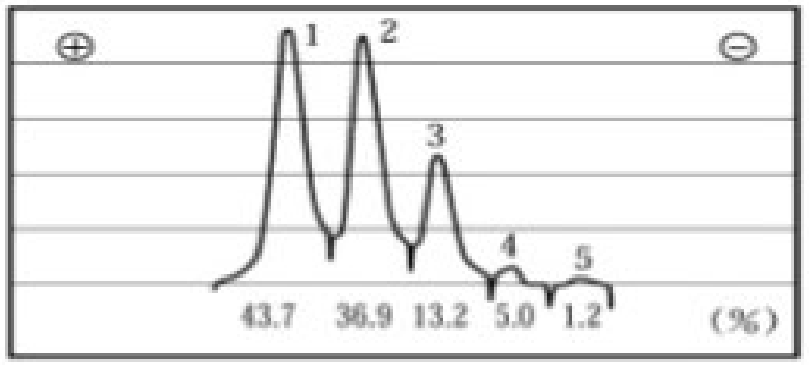
NORMAL

Flipped pattern indicative of MI

LD-1 > LD-2

-or -

LD-1:LD-2 ratio >1



MYOCARDIAL INFARCTION

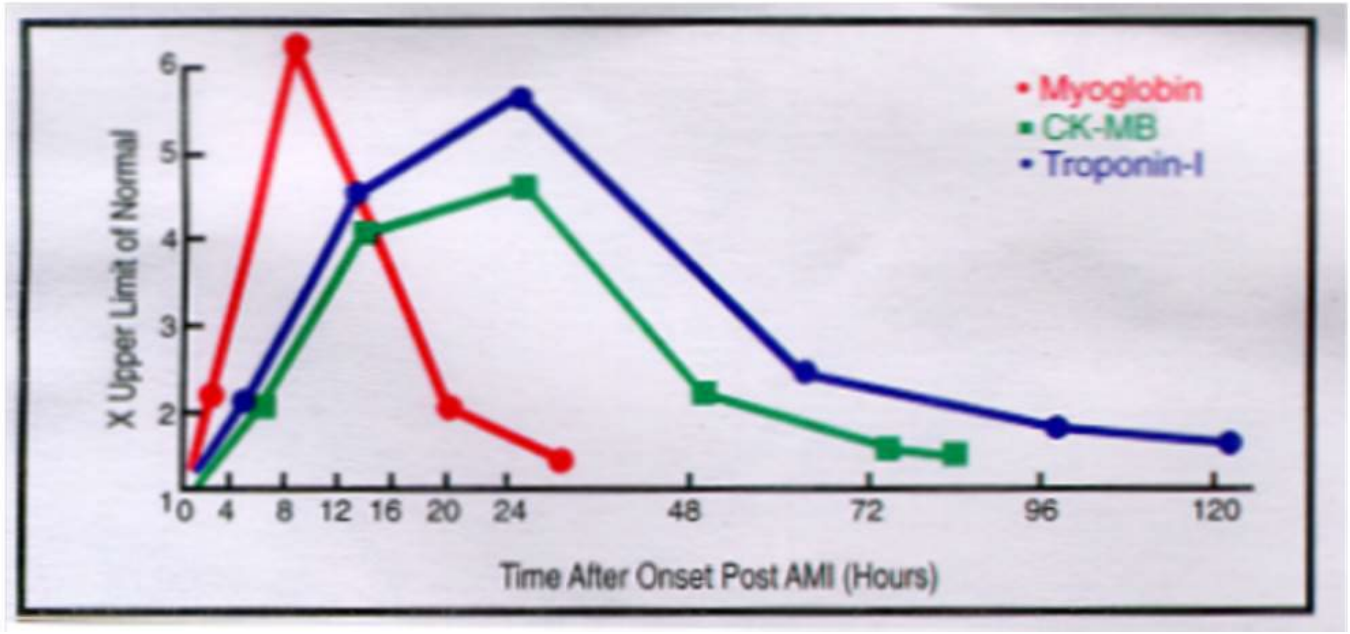
Cardiac Markers

Newer cardiac markers

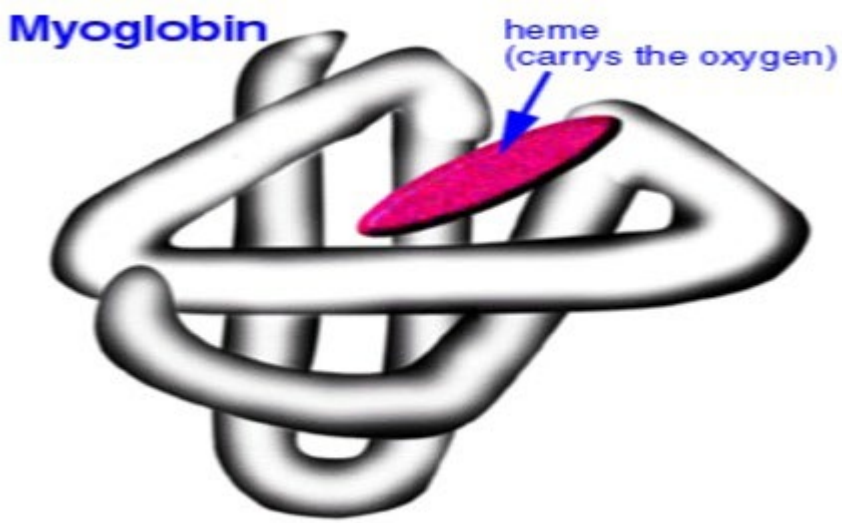
CK-MB

Myoglobin (first marker up, first marker down)

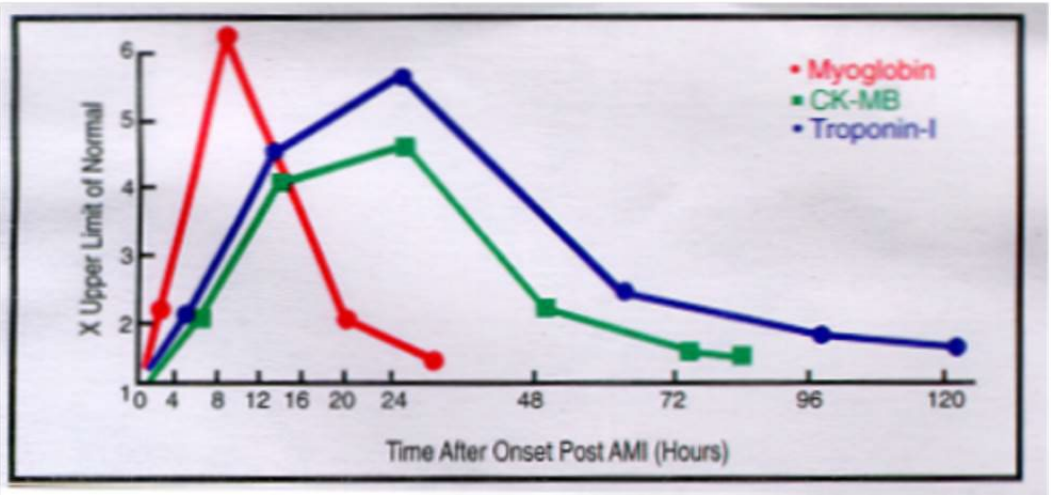
Troponin T or I



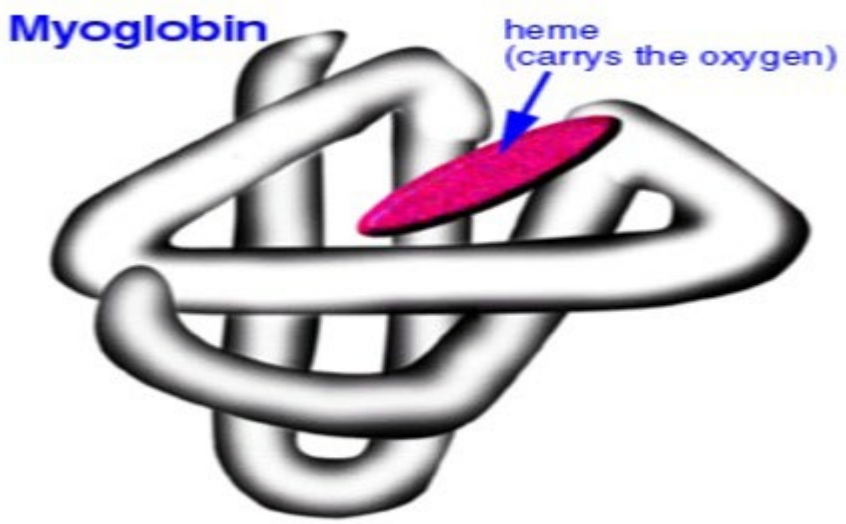
Myoglobin



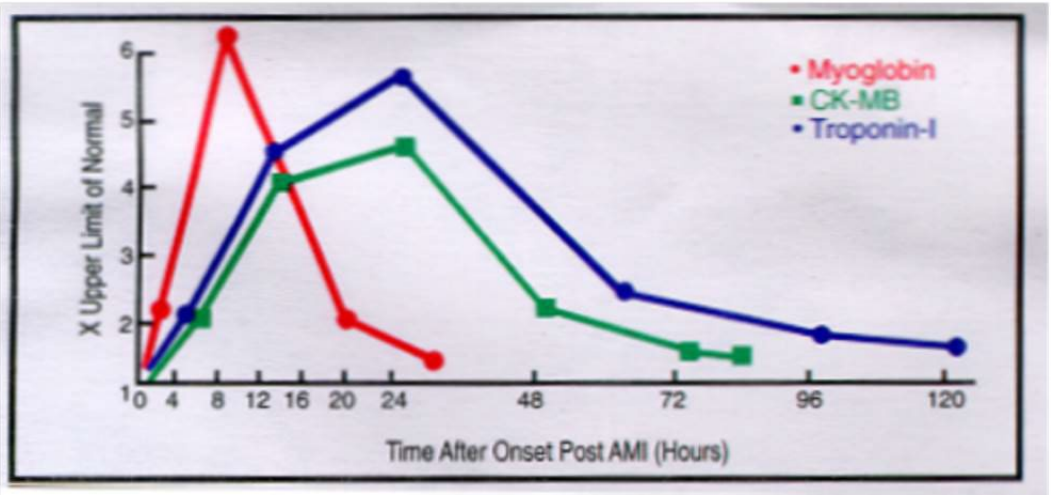
- Small, oxygen binding protein found exclusively in the muscle (cardiac **and** skeletal muscle)
- Stores oxygen within muscle cells and releases it during oxygen deprivation
- Normally absent from the circulation (presence in serum indicates muscle injury)
- Released very quickly when muscle is damaged



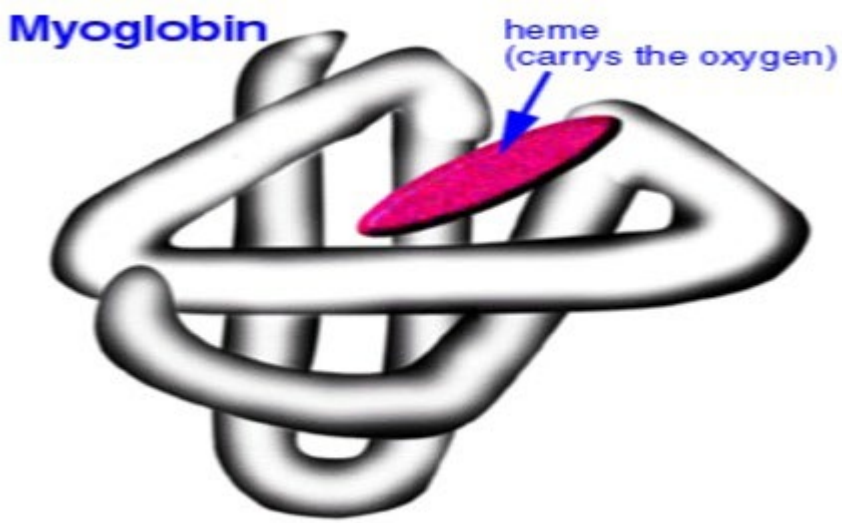
Myoglobin



- Earliest biomarker to rise after myocardial infarction
- Appears in blood within 1-2 hours after onset of chest pain
- Peaks at 6-9 hours and returns to baseline within 24 hours
- **Methodology**: immunoassay (most common)



Myoglobin

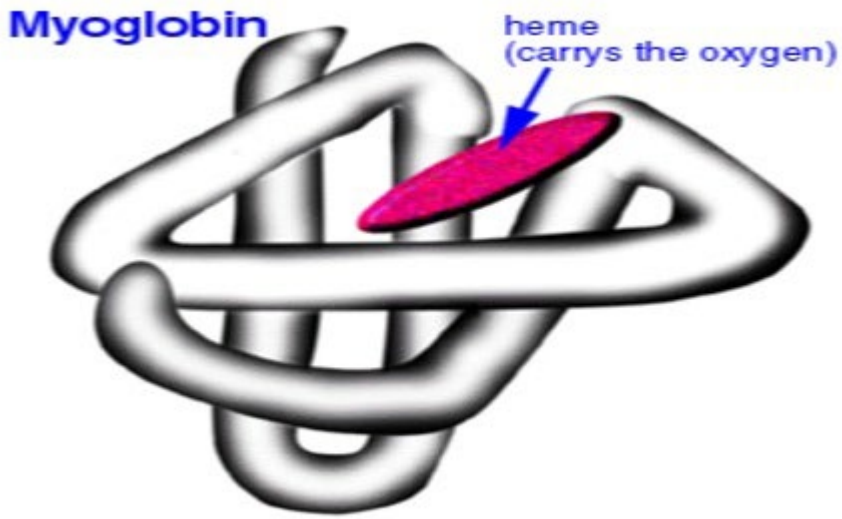


- **NOT SPECIFIC FOR THE HEART – False positives can be due to skeletal muscle injuries** (trauma or crush injuries, intense exercise, muscular dystrophies)

- Absence can help rule out AMI if levels remain normal within 4-6 hours after symptom onset

- Previously used as an **early rule-out marker** for MI, but largely been replaced with high sensitivity troponin

Limitations of Myoglobin



- **Lack of specificity –** elevated in any muscle injury (cardiac and skeletal)
- **Short diagnostic window** – returns to normal quickly so may miss delayed presentations
- **Myoglobin cleared by kidneys** – renal failure → falsely high levels
- **Superseded by high sensitivity troponin**

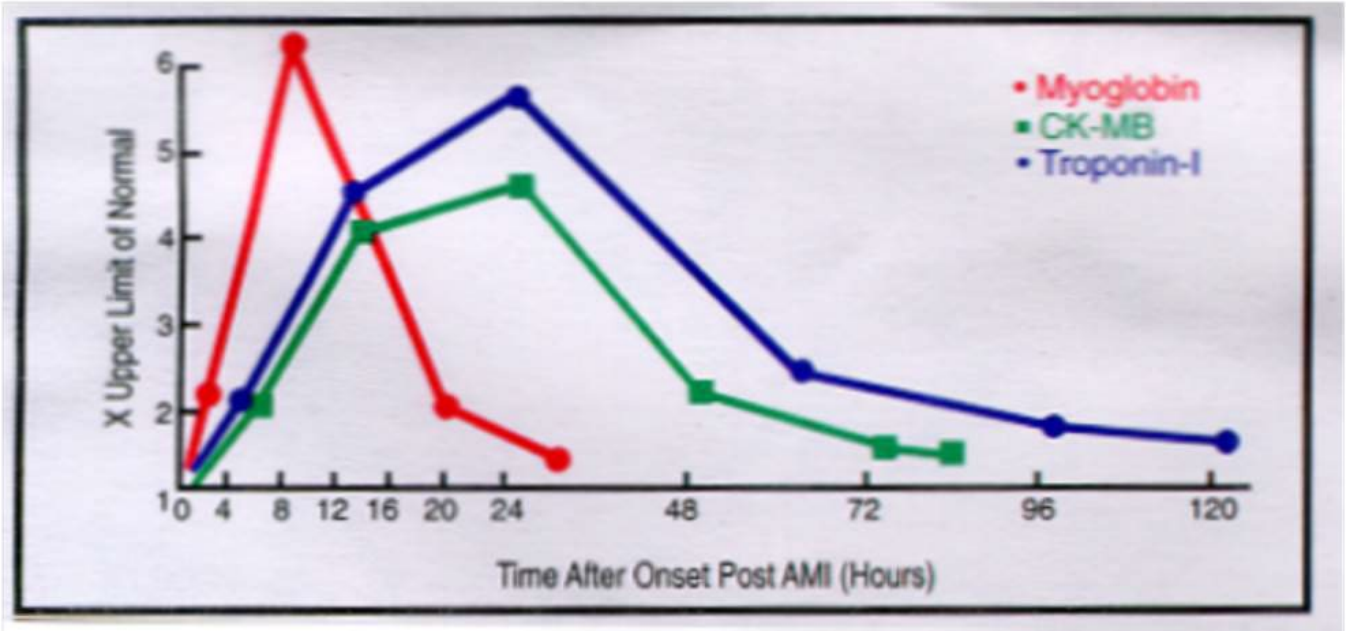
Cardiac Markers

Newer cardiac markers

CK-MB

Myoglobin (earliest, not heart specific; returns to normal fastest)

Troponin T or I



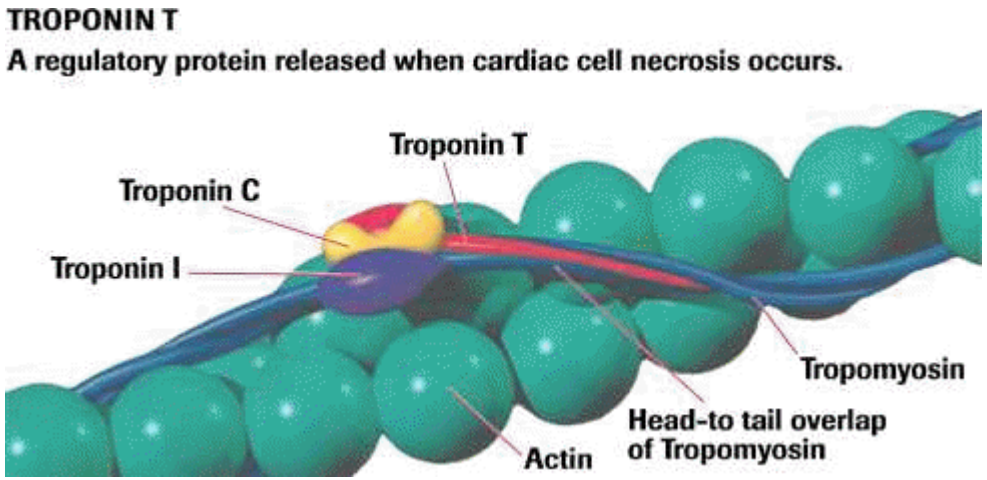
Troponin

Commonly considered the new “gold standard” for diagnosis of myocardial infarction

Complex of 3 proteins in striated muscle (skeletal and cardiac)

- Troponin T (TnT)
- Troponin I (TnI)
- Troponin C (TnC)

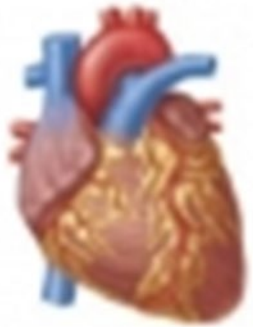
Controls muscle contraction



3 Troponin Isoforms

Troponin I and T have 3 tissue-specific isoforms in:

- Slow-twitch skeletal muscle
- Fast-twitch skeletal muscle
- Cardiac muscle
  (released after myocardial damage)

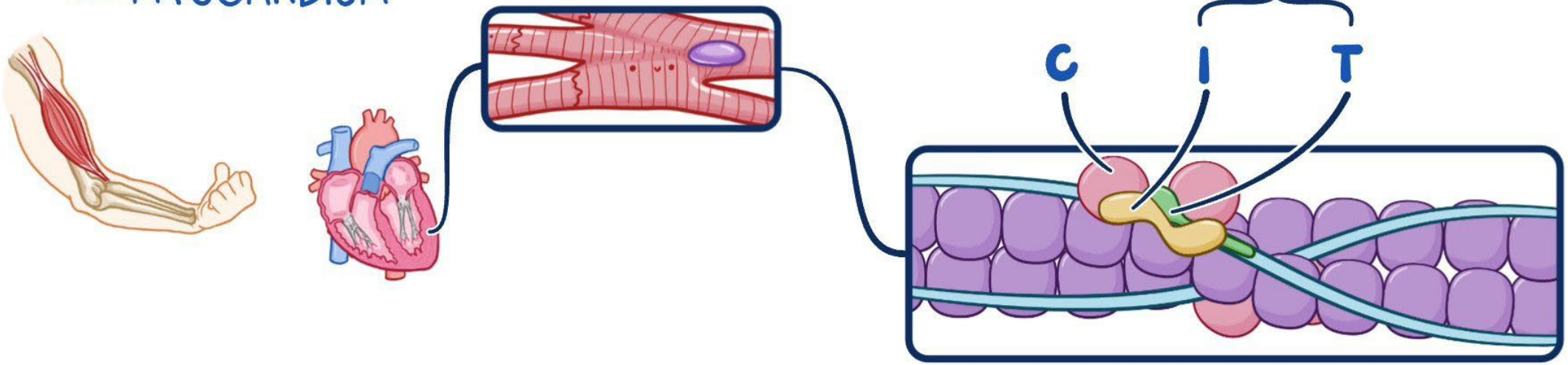


Allows for highly specific measurement of troponin of cardiac origin (cTnT and cTnI)

PHYSIOLOGY

TROPONIN

~ PROTEIN FOUND in STRIATED MUSCLE
- SKELETAL MUSCLES
- MYOCARDIUM



CARDIAC TROPONINS (cTn)

~ HIGHLY SPECIFIC to MYOCARDIAL TISSUE

The cardiac isoforms are commonly just called troponin T and troponin I

What’s normal?

- Circulating levels of cardiac troponins are normally extremely low
- Normal levels of circulating cTnI are <0.04 ng/mL
- When cardiac muscle cells are injured, troponin is released into the bloodstream

Troponin Window of Detection

- Most beneficial in identifying a heart attack 6 or more hours after symptom onset
- Peak at 12-24 hours
- Remains detectable for up to 2 weeks
  - 8-12 days for cTnT
  - 7-14 days for cTnI
- Cardiac troponins thus offer the widest window for detection post-MI

Feature	Myoglobin	CK-MB	Troponin
Tissue specificity	Skeletal + cardiac	Cardiac > skeletal	Cardiac only
Rise (hours)	1-2	3-6	3-4
Peak (hours)	6-9	12-24	12-24
Return to normal	24 hours	2-3 days	7-14 days
Usefulness	Early indicator, rule out	Useful for detecting reinfarction after troponin remains elevated	Gold standard for AMI

Case Study

- 58 year-old male with crushing chest pain radiating to the left arm
- Onset: ~1.5 hours prior to hospital arrival
- Additional symptoms: shortness of breath, diaphoresis, nausea
- History: hypertension, hyperlipidemia, current smoker

Time After Onset	Troponin I (ng/mL)	CK-MB (ng/mL)	Myoglobin (ng/mL)
1.5 hours (admission)	0.012	1.8	160 (↑)
3 hours	0.115 (↑)	8.5 (↑)	380 (↑)
6 hours	0.420 (↑↑)	20 (↑↑)	250 (↓)
24 hours	0.780 (*peak*)	25 (*peak*)	110 (↓)
48 hours	0.230 (*falling*)	6 (*falling*)	25

- **Troponin** shows a typical rise and fall pattern with peak ~24 hours (consistent with AMI)
- **CK-MB** follows a similar pattern
- **Myoglobin** increases earliest (but lacks cardiac specificity)
- **CK-MB** and **myoglobin** support the early diagnosis and trend confirmation shown by troponin

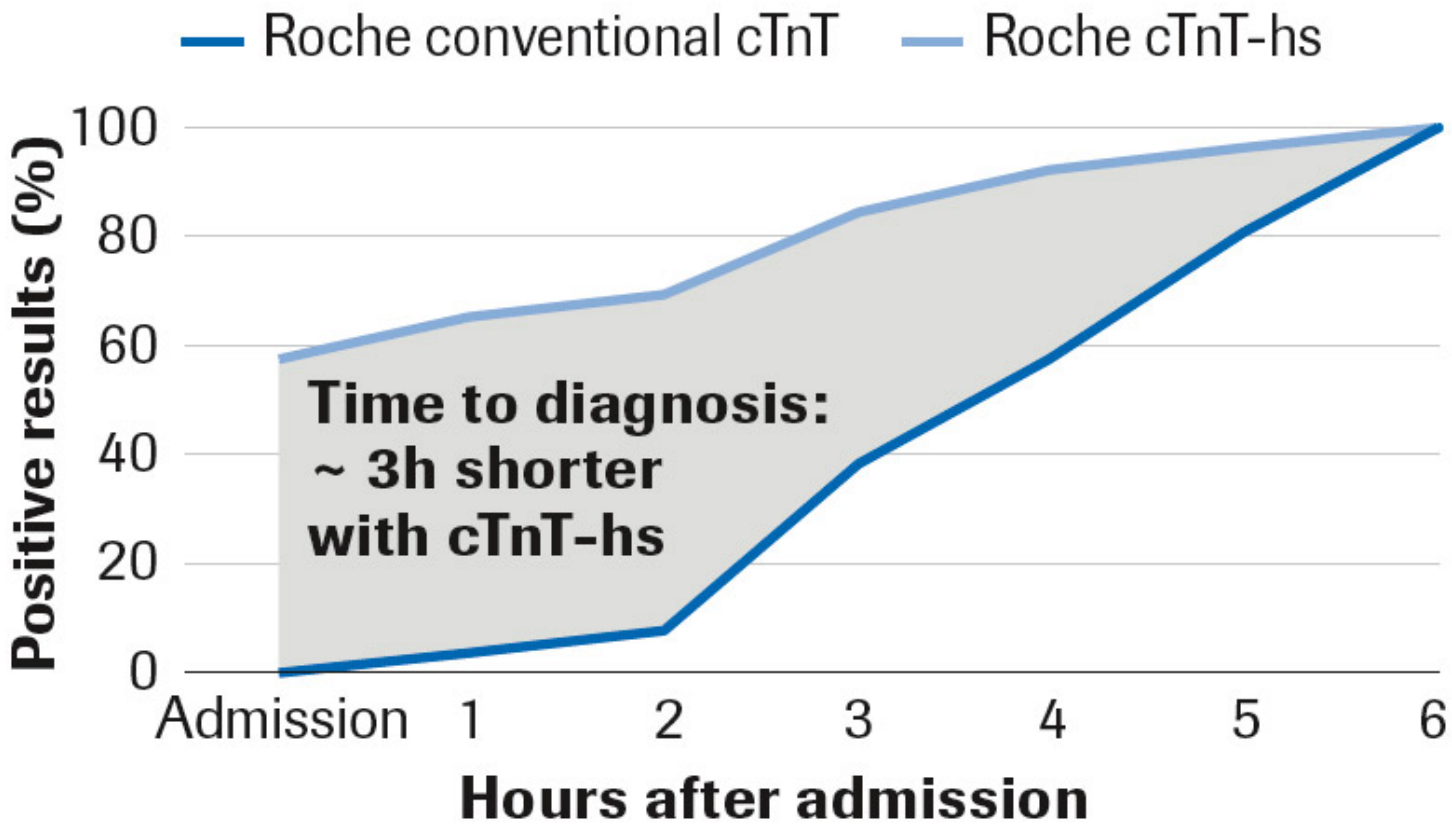
High Sensitivity Troponin

Standard cardiac troponins may not be detected when a patient presents early with chest pain (<2 hours)

hs-cTn assays can confirm myocardial injury at **very low concentrations** and identify smaller increases in concentration within the normal reference range

Normal levels of circulating hs-cTn are <0.014 ng/mL

High Sensitivity Troponin



Newer high sensitivity troponin assays are now approved in U.S.

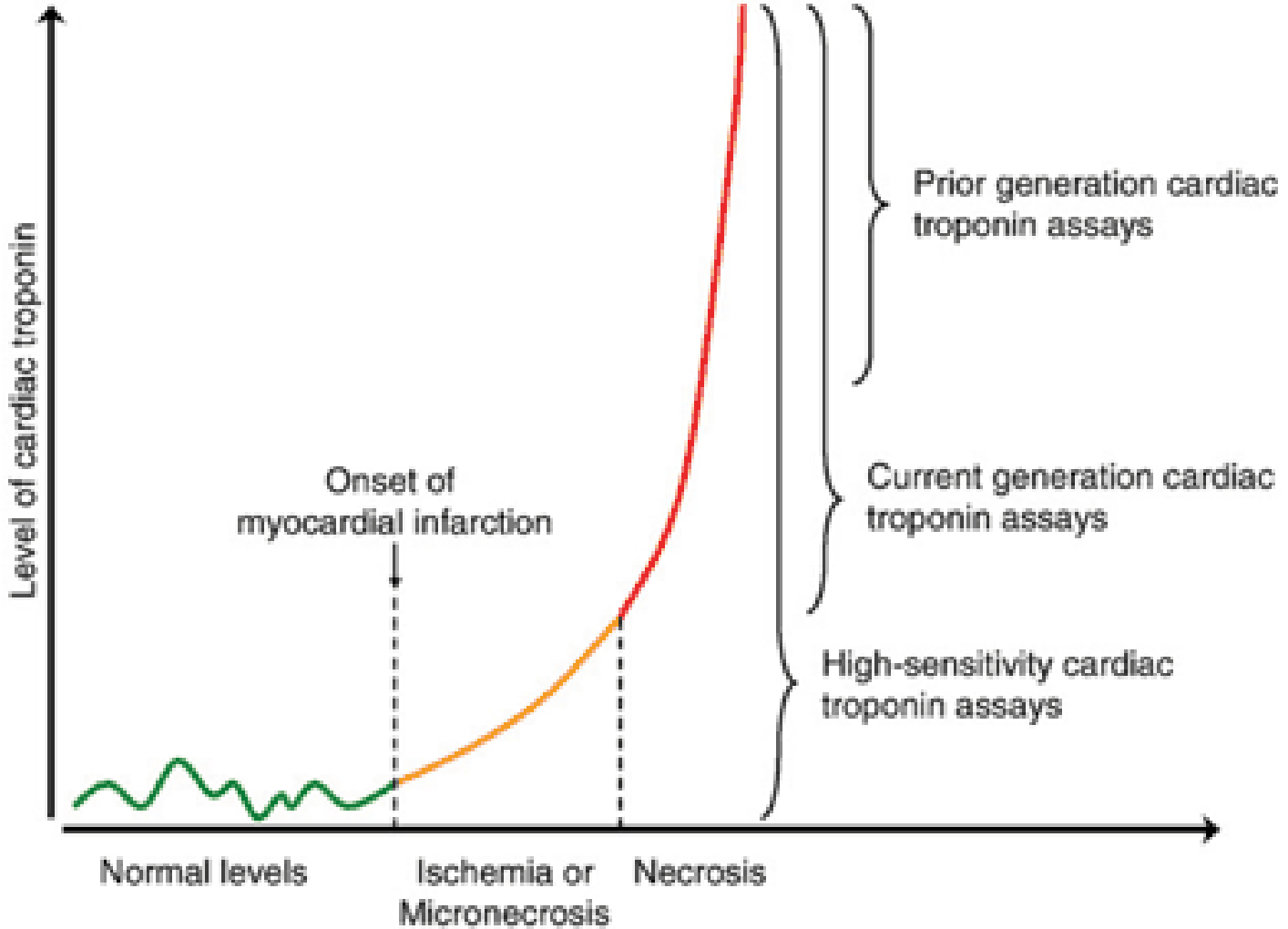
High Sensitivity Cardiac Troponin T: Its Finally Here!

Nam K. Tran, PhD, HCLD (ABB), FACB, Associate Professor and Director of Clinical Chemistry

Introduction

On June 18, 2018, UC Davis Health will transition to a “high sensitivity” (hs) cardiac troponin T (cTnT) assay (Roche Diagnostics, Indianapolis, IN). This new test is presently the only hs-troponin test available in the United States[1] and UC Davis will presently be the only institution in Northern California to offer this test. The hs-cTnT assay is also faster and exhibits enhanced analytical precision to enable short interval serial testing for emergency department (ED) patients.

Troponin Assays



*Current generation assays detect rising cTn levels indicative of MI. High-sensitivity assays detect lower levels reflective of ischemia micronecrosis and even normal cell turnover.

Ischemia Modified Albumin (IMA)

Does not detect muscle damage

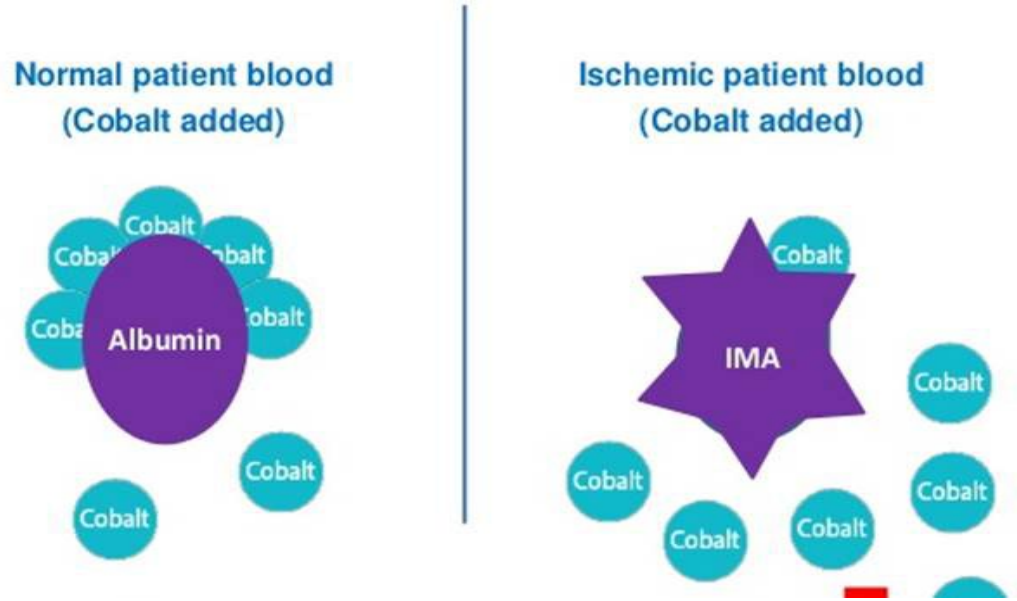
In ischemic conditions, albumin loses ability to bind metals (basis for testing)

Detects changes that occur in albumin in presence of ischemia (happens within 10-30 minutes, before cell death occurs)

Can be used in conjunction with troponin and EKG for early detection of myocardial ischemia

IMA Interpretation

< 80 U/mL	normal
80-100 U/mL	borderline/possible ischemia
>100 u/mL	suggestive of myocardial ischemia



In ischemic conditions, albumin loses ability to bind metals (basis for testing)

Case Study

55 year-old male with chest pain for 30 minutes, normal EKG, normal troponin

Marker	Time	Result	Interpretation
IMA	0.5 hr	115 U/mL (↑)	Suggests early ischemia
Troponin I	0.5 hr	<0.04 ng/mL	Normal
Troponin I	3 hr	0.130 ng/mL (↑↑)	Confirms MI
EKG	ST elevation (later)		MI confirmed

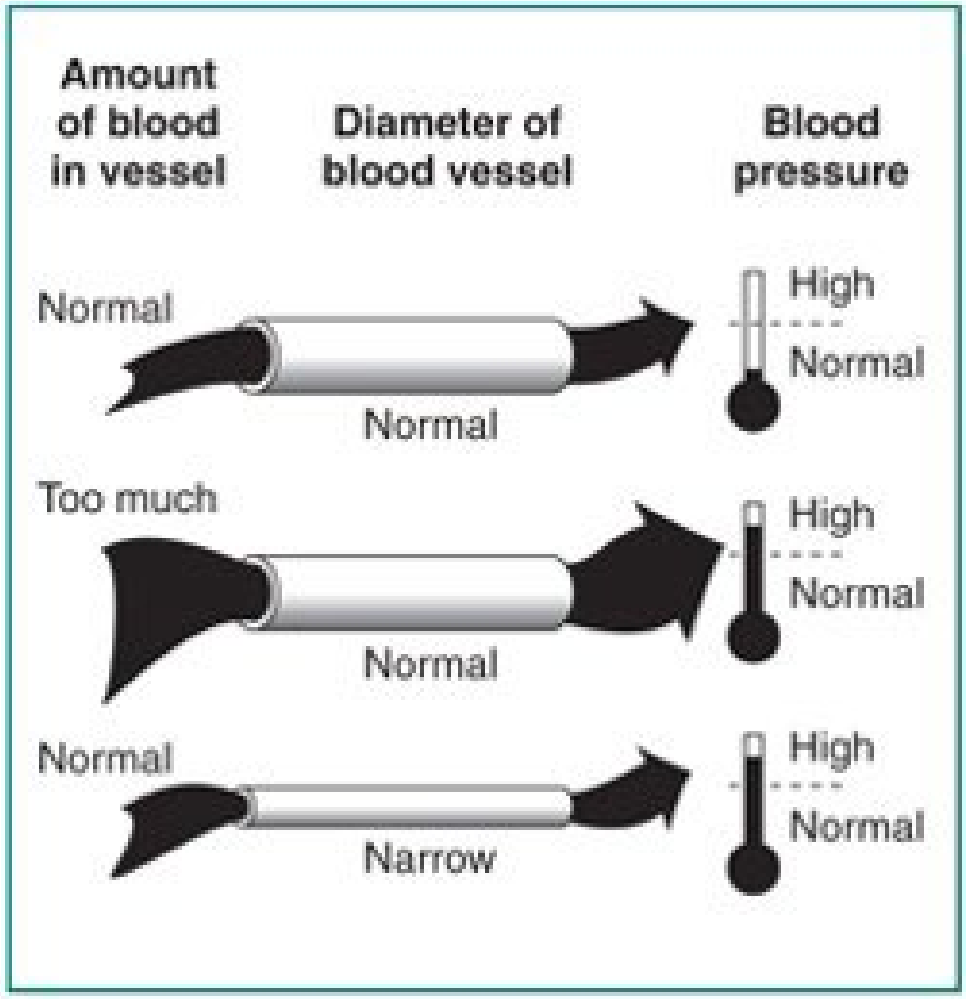
Blood Pressure

Blood pressure

Affected and controlled by two things:

1. Blood volume

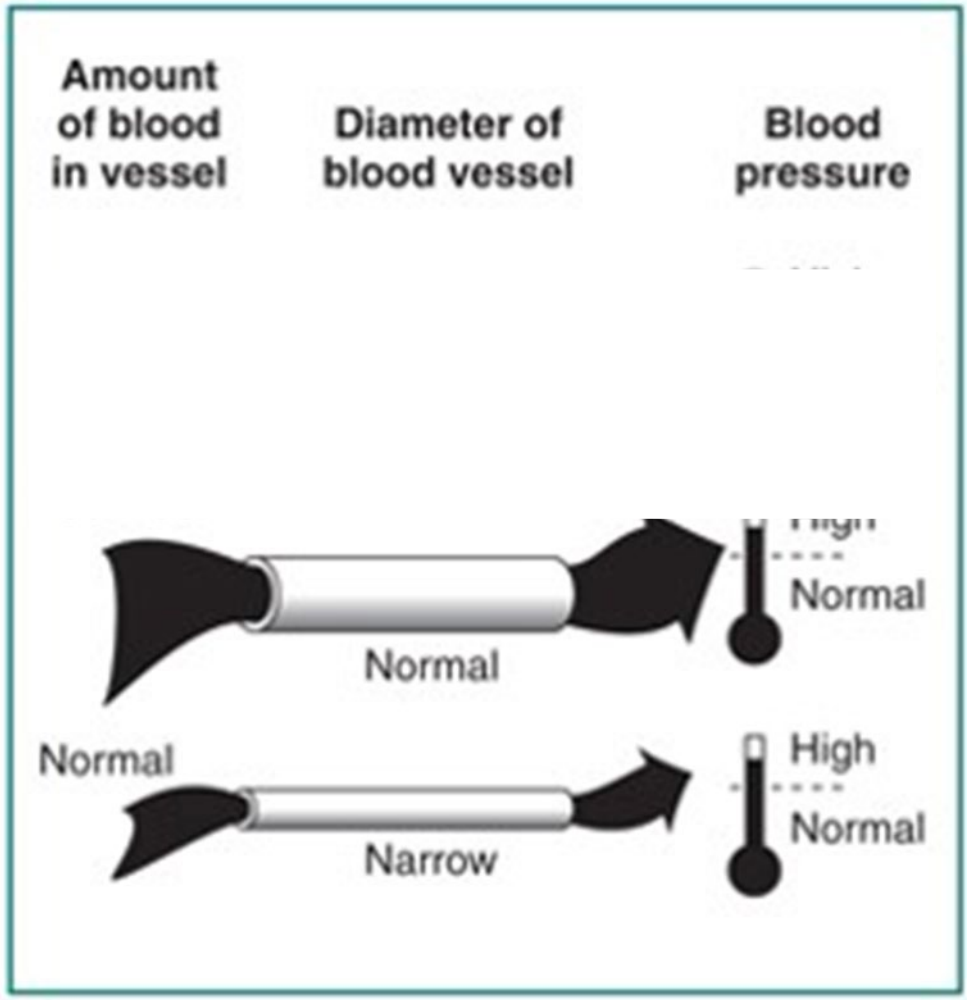
2. Vessel diameter



Renin-Angiotensin-Aldosterone System (RAAS)

RAAS is the body's primary long-term mechanism for maintaining blood pressure and fluid balance.

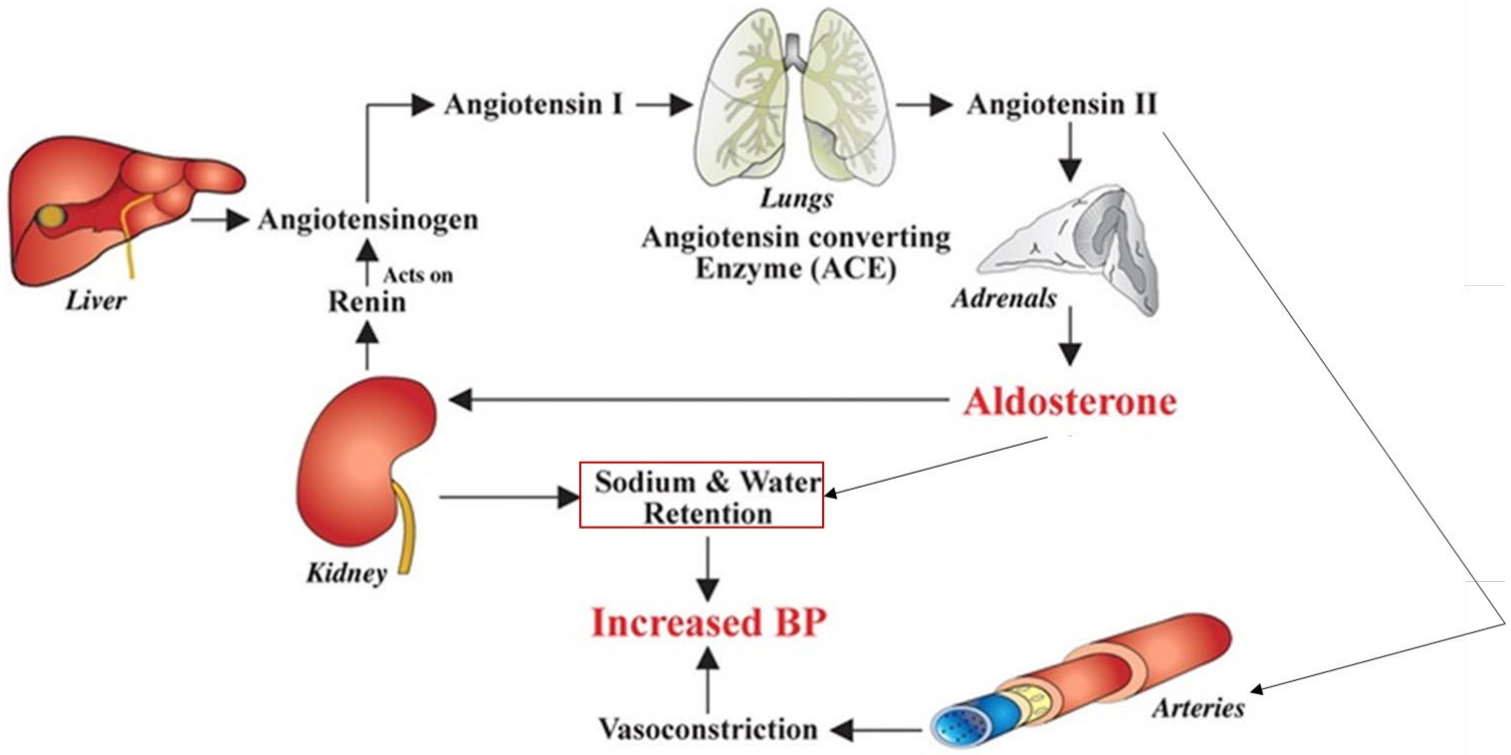
It connects the kidneys, liver, lungs, and adrenal glands.



Renin

- Enzyme produced by kidneys

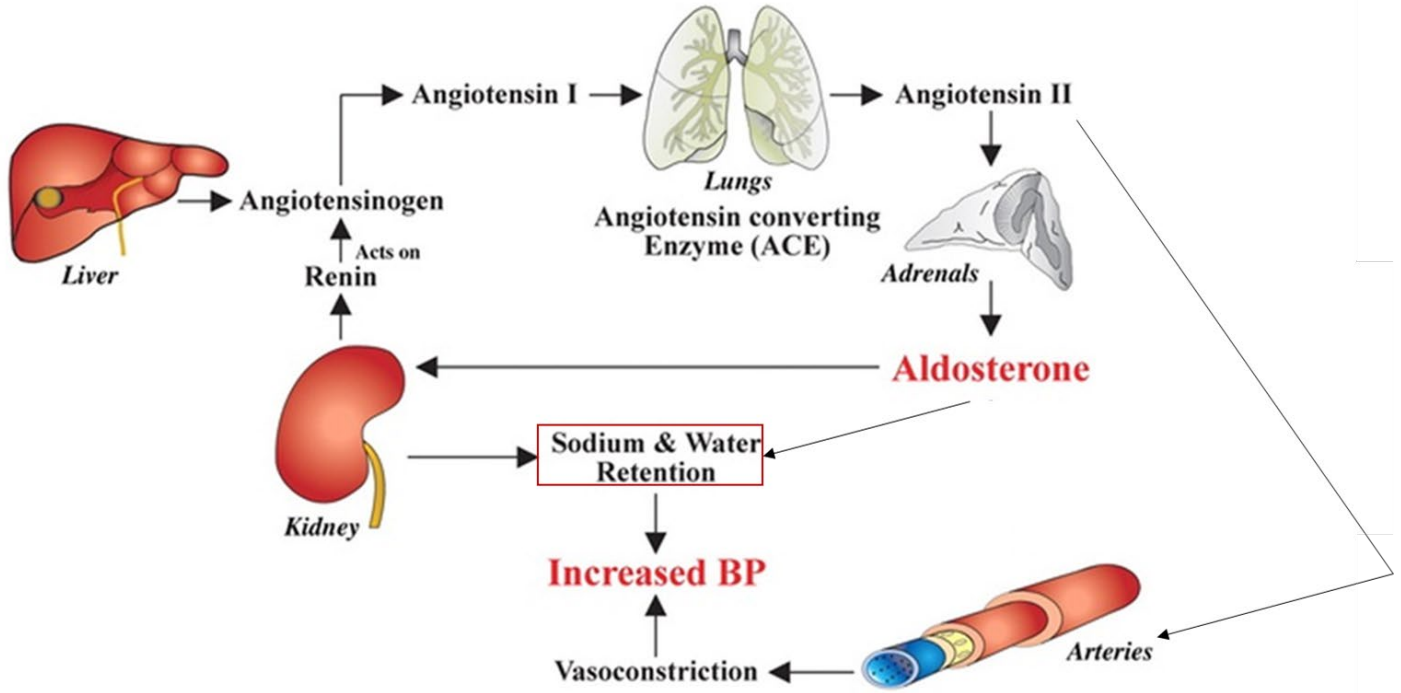
- Secreted in response to
  ↓ serum sodium or
  ↓ blood pressure



Renin

- Converts angiotensinogen (protein produced by the liver) into angiotensin I

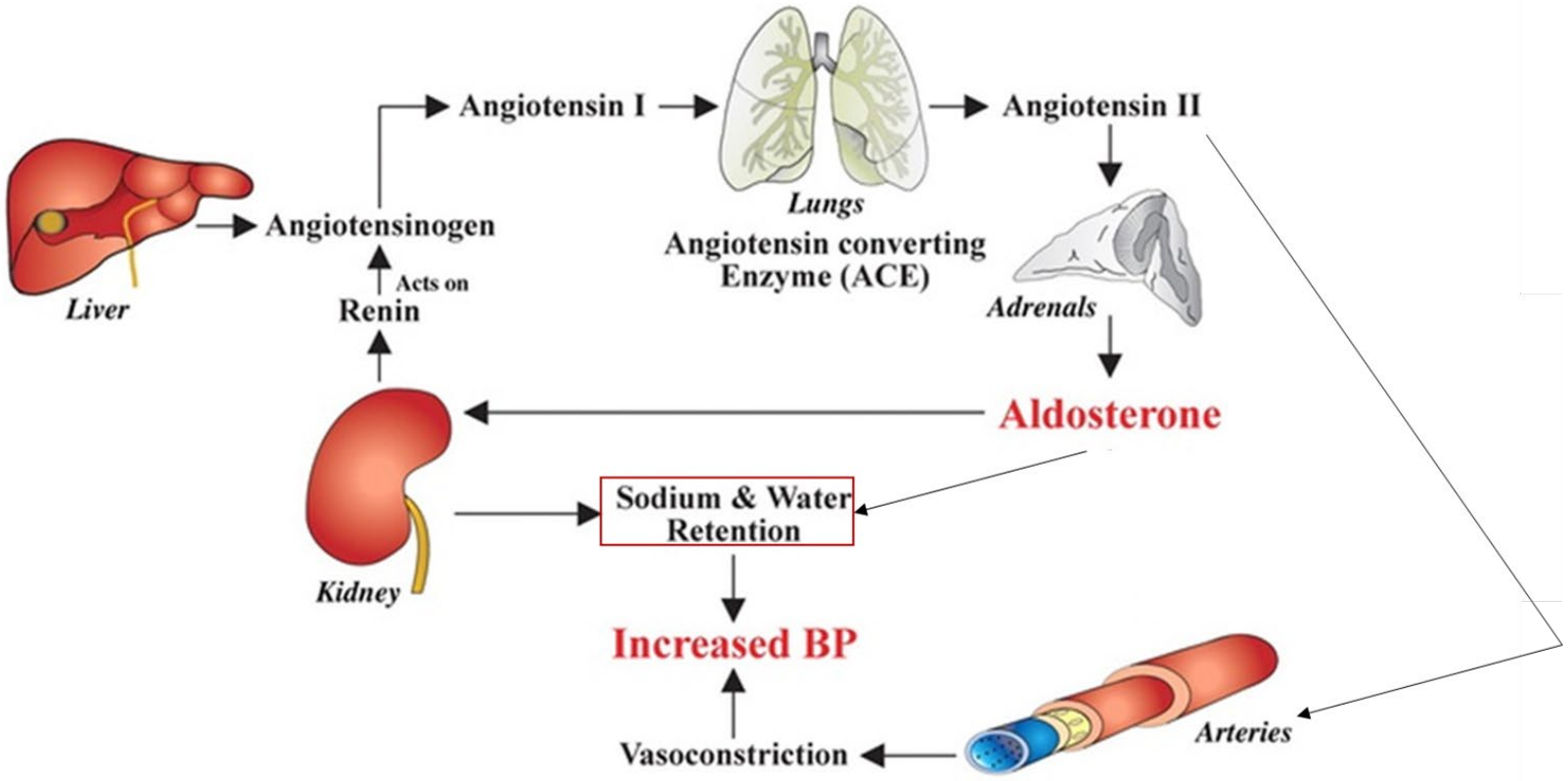
- Angiotensin I (inactive form) is then converted to angiotensin II (active form) by ACE in the lungs



Angiotensin II

Causes vasoconstriction

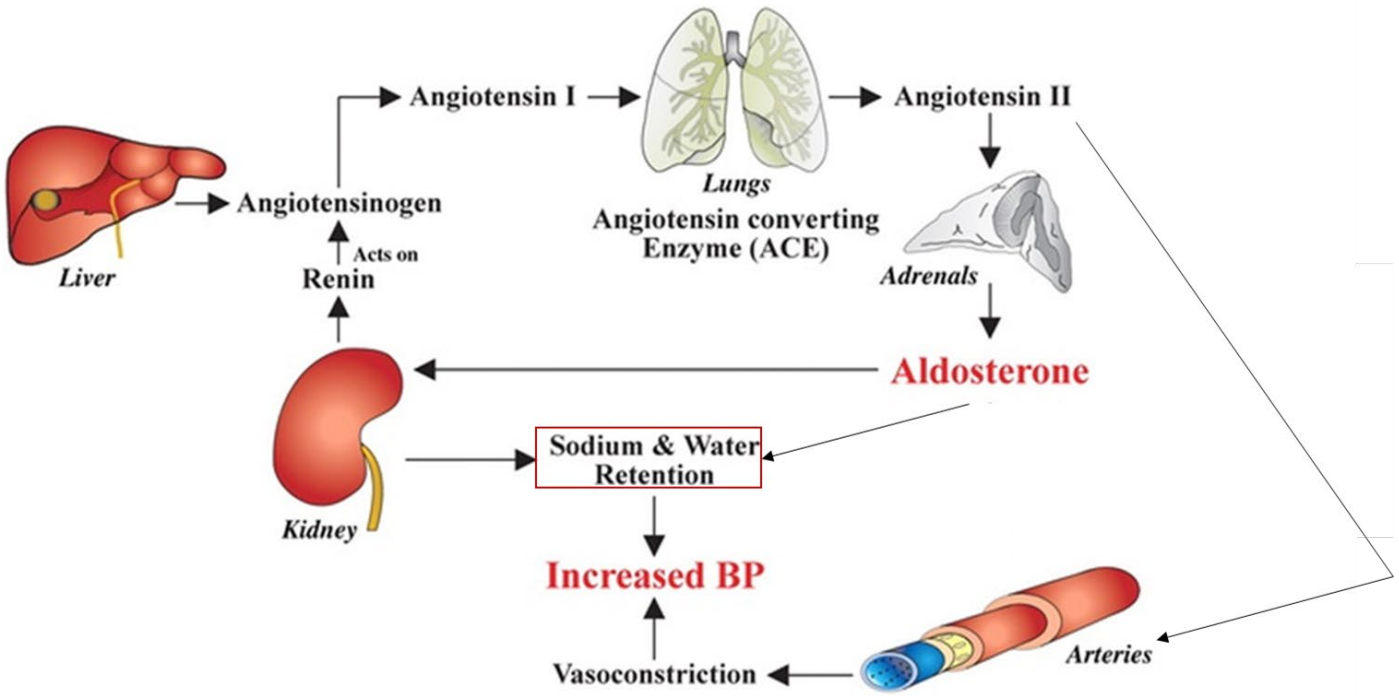
Stimulates the adrenal glands to secrete aldosterone



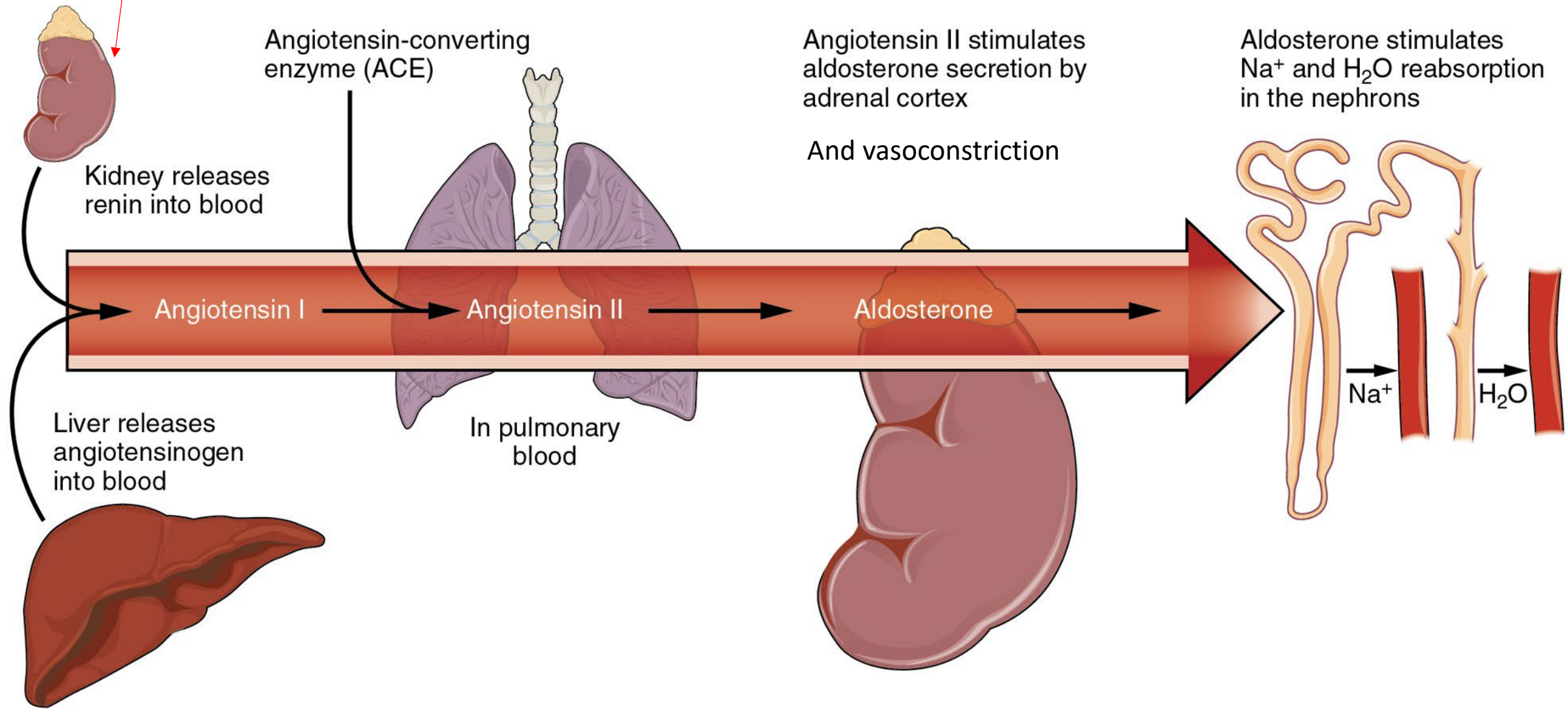
Aldosterone

Increases sodium and water reabsorption in kidneys → increased blood volume

Increased blood volume → increased blood pressure



Low serum Na or
Decreased renal perfusion



Related Lab Tests- Patients with high blood pressure

Renin

Aldosterone

Electrolytes

Congestive Heart Failure

Heart unable to efficiently pump blood

Fluid retention, **shortness of breath**, fatigue, lower body edema

Can be difficult to diagnose - feel run down; minor exertion leaves them out of breath

Natriuretic Peptides

- A family of hormones that affect body fluid homeostasis through:
  - natriuresis (excretion of sodium in urine)
  - diuresis (increased production and excretion of urine), and
  - Vasodilation (through decreased angiotensin II)

- Includes:
  - Atrial natriuretic peptide (ANP)
  - **B-type (or brain) natriuretic peptide (BNP)**
  - C-type natriuretic peptide (CNP)
  - Dendroaspis natriuretic peptide (DNP)

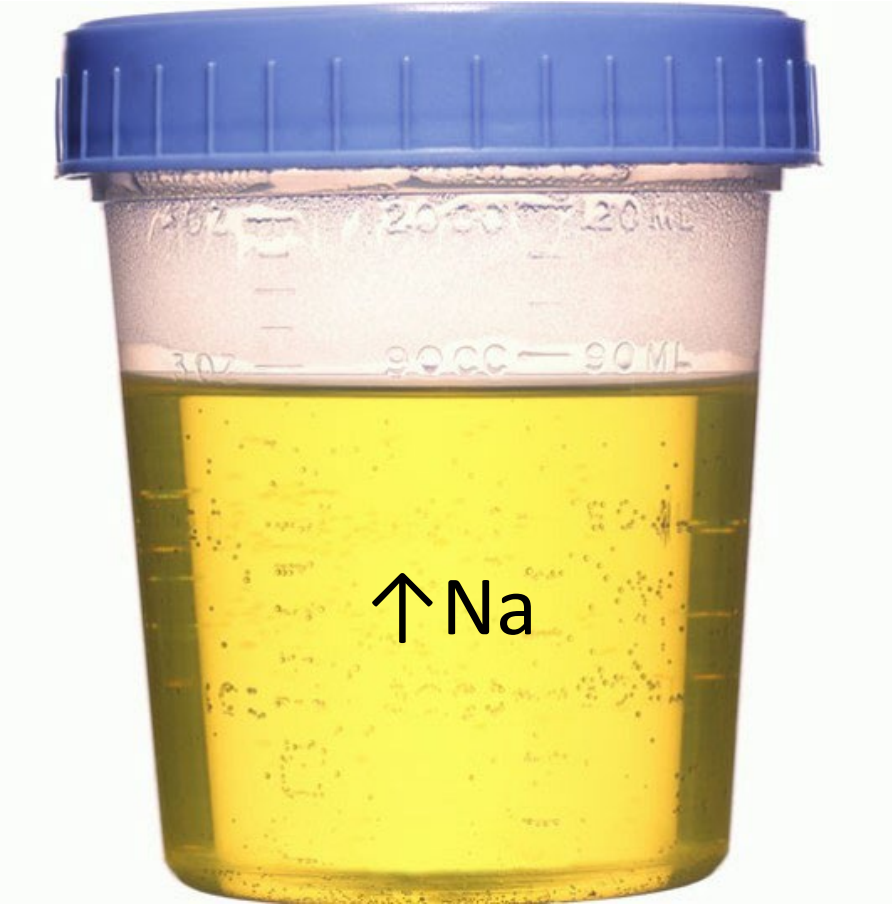
BNP (B-type nartriuretic peptide)

Helpful in determining cardiac vs. pulmonary causes of SOB

Released from cardiac cells in response to the ventricles stretching (from increased pressure and volume load)

Physiological antagonist to RAAS

Decreases blood pressure by <u>vasodilation</u> and urinary excretion of sodium and water (<u>decreases blood volume</u>)



BNP Effect	Opposes RAAS Action
Vasodilation	↓ vasoconstriction
↑ sodium excretion (natriuresis)	↓ sodium retention
↓ aldosterone secretion	↓ volume expansion
↓ thirst and ADH release	↓ fluid retention

In **heart failure**, high BNP = chronic overactivation of RAAS

BNP Production

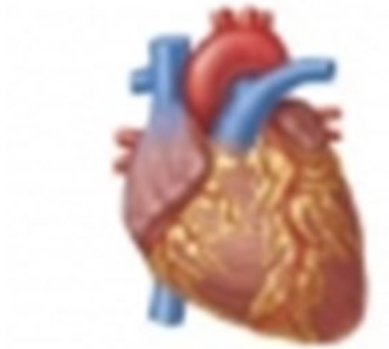
Heart ventricle myocytes produce the prohormone, proBNP

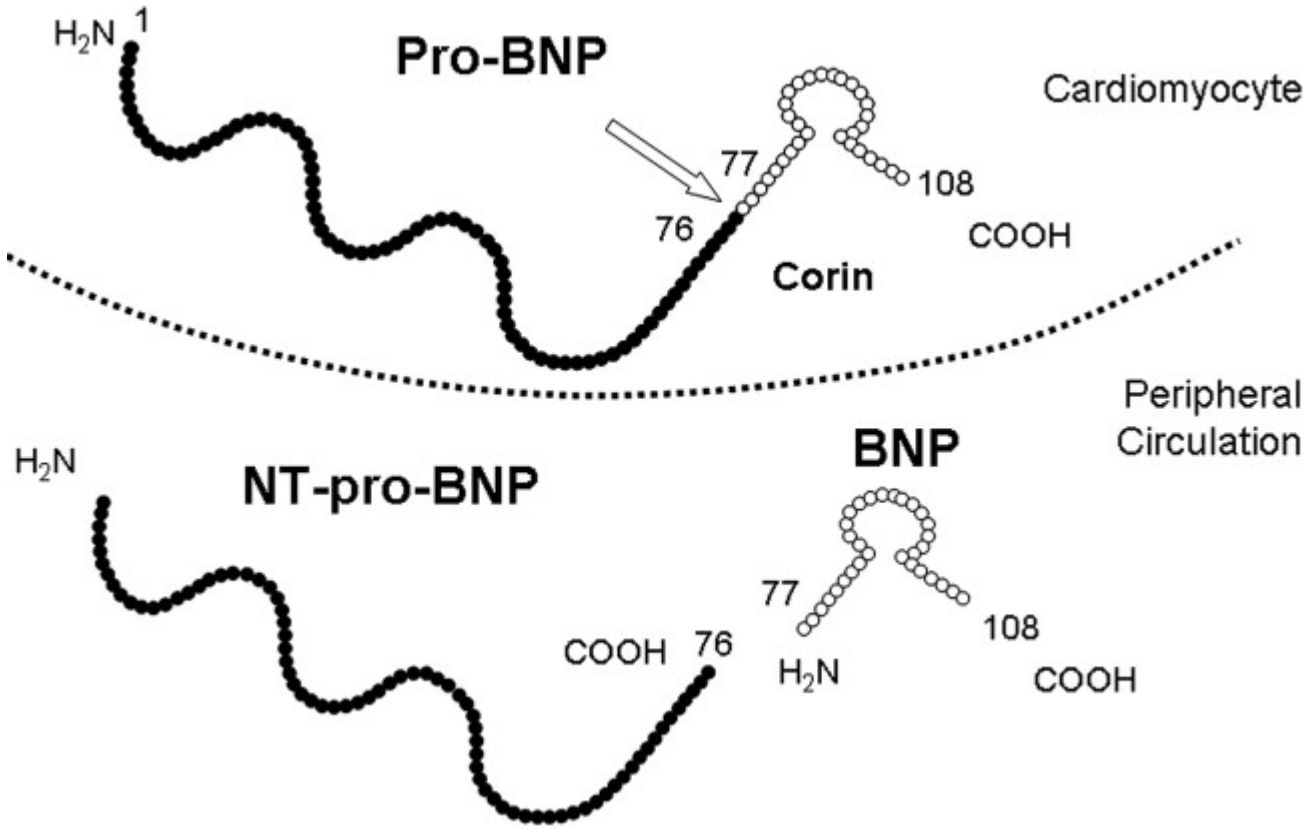
↓

Hypertension and volume overload cause ***tension and stretching of walls***

↓

Produces the enzymes corin and furin, which cleave proBNP → N-terminal (NT)-proBNP and BNP





BNP and NT-proBNP

BNP - biologically active portion

NT-proBNP - biologically inactive portion (but more stable in plasma)

Both are used in clinical laboratories to diagnose and monitor CHF.

Both reflect the same underlying process – myocardial wall stress.

Reference ranges are not interchangeable.

BNP and NT-proBNP

	BNP	NT-proBNP
Molecule Type	Active hormone	Inactive fragment
Half-life	Short (~20 minutes)	Longer (~60-120 minutes)
Stability	Less stable in plasma	More stable (preferred for sample transport/storage)
Assay Variability	Different assays use different antibodies → possible variability	More standardized and consistent across platforms

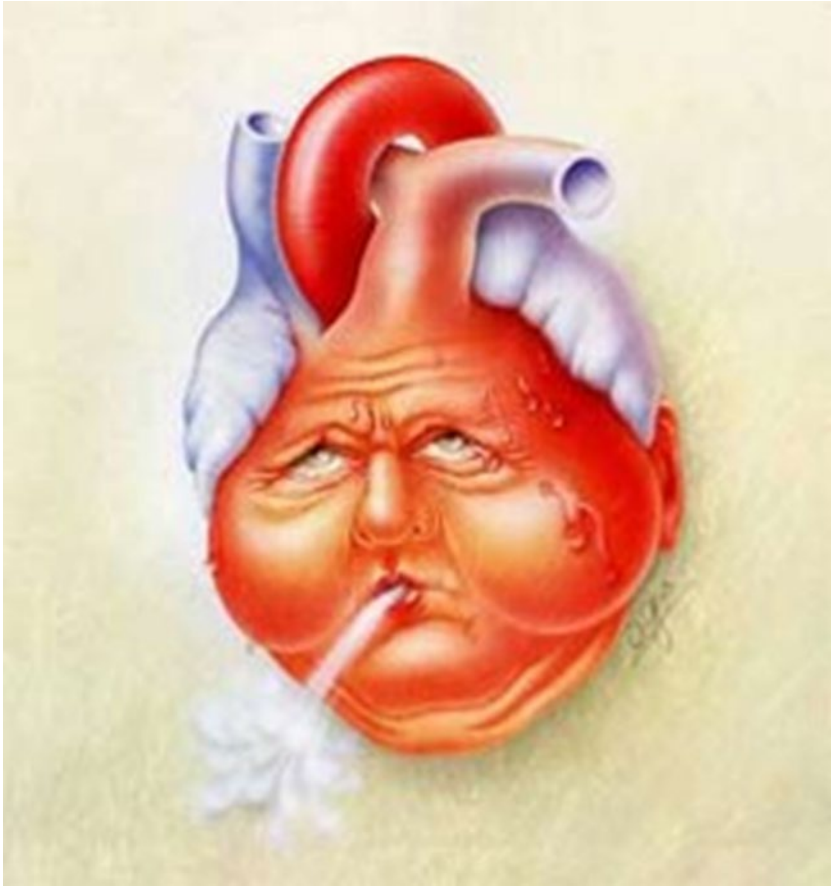
BNP and CHF

Lab tests for BNP or NT-proBNP are used primarily to diagnose and assess the severity of Congestive Heart Failure (CHF)

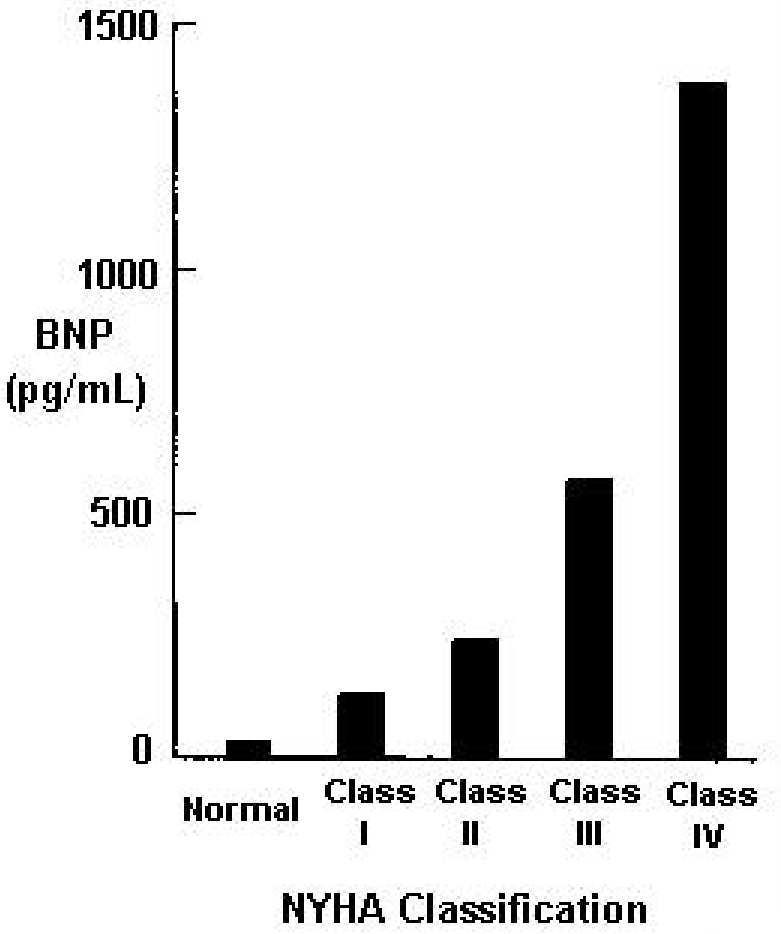
BNP and NT-proBNP **rise with heart failure severity**

Higher BNP → higher morbidity and mortality

Cutoff for CHF in most studies: 100 pg/mL



BNP and Congestive Heart Failure



Source: Biosite Digagnostics

Class I

No limitations of physical activity. No fatigue, shortness of breath, or heart palpitations with ordinary physical activity.

Class II

Slight limitation of physical activity. Fatigue, shortness of breath, or heart palpitations with ordinary physical activity, but patients are comfortable at rest.

Class III

Marked limitation of physical activity. Fatigue, shortness of breath, or heart palpitations with less-than-ordinary physical activity, but patients are comforable at rest.

Class IV

Severe to complete limitation of physical activity. Fatigue, shortness of breath, or heart palpitations with any physical activity, and symptoms appear even when patient is at rest.

Markers for Cardiovascular Risk Stratification

- Cardiac troponins
- hs-CRP
- Homocysteine

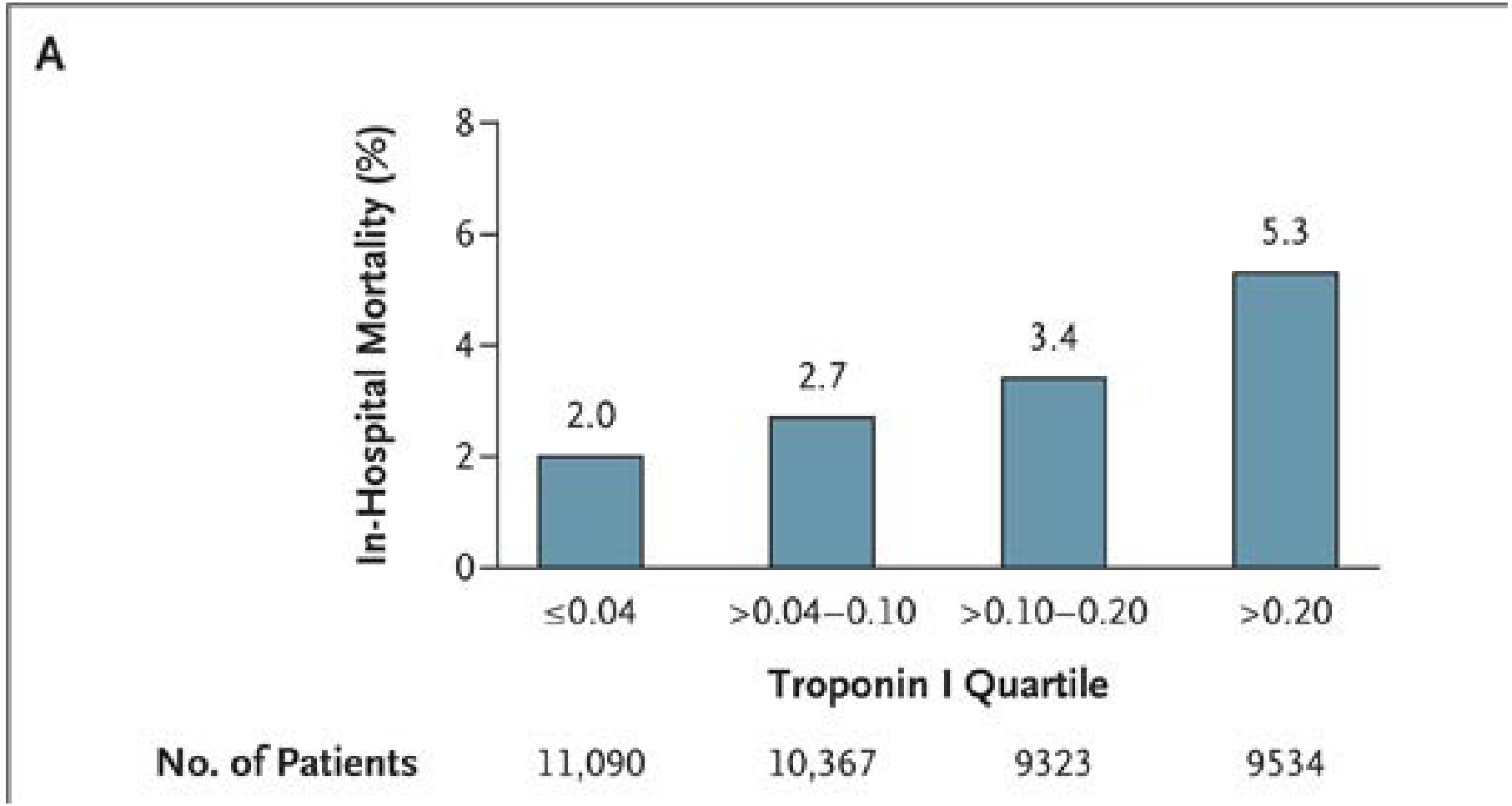
Cardiac Troponins for Risk Stratification

One of the strongest predictors of mortality, particularly if used in conjunction with BNP levels

Higher troponin = greater risk of mortality

Elevations in multiple markers (cTn, hs-CRP, BNP) are associated with escalating risk of major adverse cardiac events

In-Hospital Mortality According to Troponin I Quartile



Peacock WF 4th et al. N Engl J Med 2008;358:2117-2126

The NEW ENGLAND JOURNAL of MEDICINE

C-Reactive Protein (CRP)

Elevated CRP is associated with systemic **inflammation**, originally used as a marker of infection

Non-specific – rises in infection, inflammation, trauma, and malignancy

Used in prognostic manner, NOT a diagnostic marker

Baseline CRP levels shown to be higher in individuals that eventually experience MI than those who do not

Typical reportable range = 10-1000 mg/L

High Sensitivity CRP (hs-CRP)

Detects **chronic low-grade inflammation,** which contributes to atherosclerotic plaque formation

hs-CRP may indicate:

- Endothelial dysfunction
- Plaque formation
- Increased risk of myocardial infarction, stroke, or sudden cardiac death

High Sensitivity CRP (hs-CRP)

Measurements above heathy values, but lower than in infection, can be used as a prognostic marker of atherosclerotic processes

Measures chronic, low levels of inflammation (values <10mg/L)

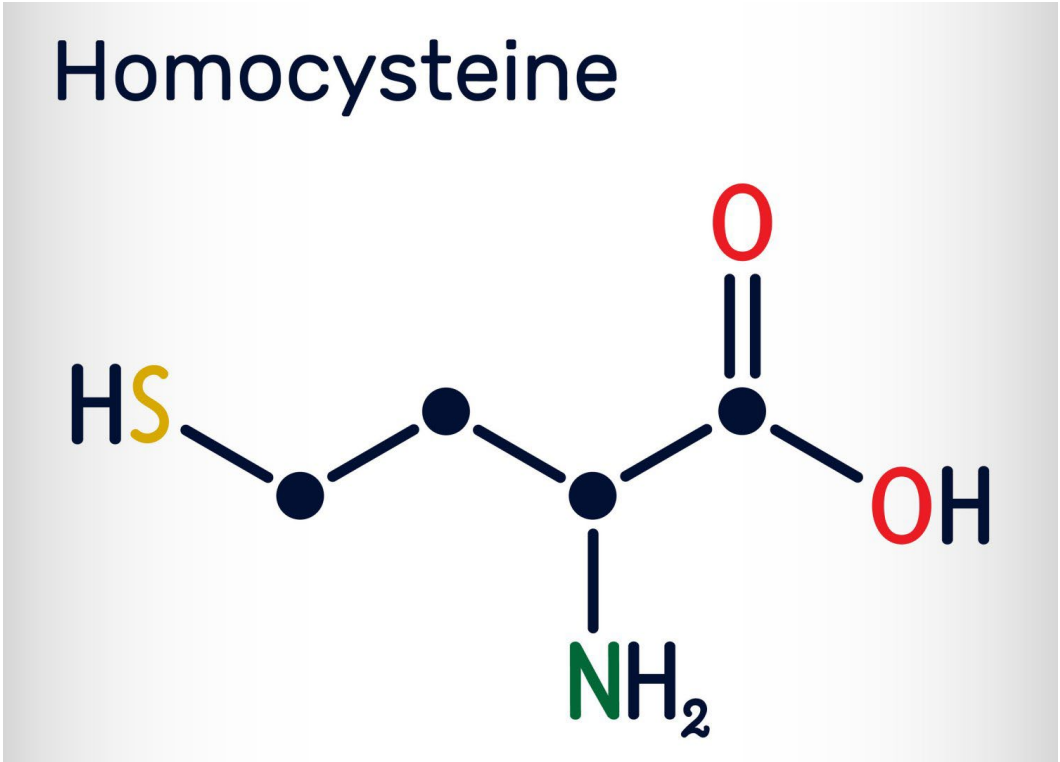
Becoming marker of choice for evaluating cardiac heart disease risk

hs-CRP Value	Cardiovascular Disease Risk Level*
< 1 mg/L	**low** risk
1-3 mg/L	**average** risk
> 3 mg/L	**high** risk

* Risk levels published in 2003. American Heart Association / Centers for Disease Control and Prevention Scientific Statement

Homocysteine

- Sulfur-containing amino acid
- Elevated levels → endothelial damage, oxidative stress, atherosclerosis, and thrombosis
- Can be used as a cardiovascular risk marker
  - atherosclerosis
  - coronary artery disease
  - stroke
  - peripheral arterial disease
- Use alongside hs-CRP for comprehensive risk assessment



Pulmonary Embolism

- Embolus = a mass that travels through the bloodstream and can cause blockages in blood vessels
- Pulmonary embolism (PE) = condition in which an embolus becomes lodged within the pulmonary arteries, impairing blood flow
- Classical presentation = **chest pain**, **shortness of breath**, tachycardia, tachypnea, and coughing
- Imaging is required to <u>confirm</u> diagnosis, but…

D-dimer

- Sensitive marker of fibrin formation and breakdown
- Levels are abnormal in ~90% of patients with PE
- However, abnormal levels can be seen for various other reasons
  - malignancy, recent surgery, renal dysfunction, increased age
- D-dimer testing is most useful for excluding PE, rather than diagnosing it

Marker	Currently Used to Diagnose Acute MI	Currently Used to Differentiate Heart Failure from Lung Disease	Currently Used to Help Diagnose Pulmonary Embolism	Used for Cardiovascular Risk Stratification	No Longer Used or Used Less Commonly
CK-MB	X				
LDH					X
Myoglobin					X
TnI, TnT	X			X	
hs-Tn	X				
BNP, NT-proBNP		X			
hs-CRP				X	
Homocysteine				X	
D-Dimer			X		