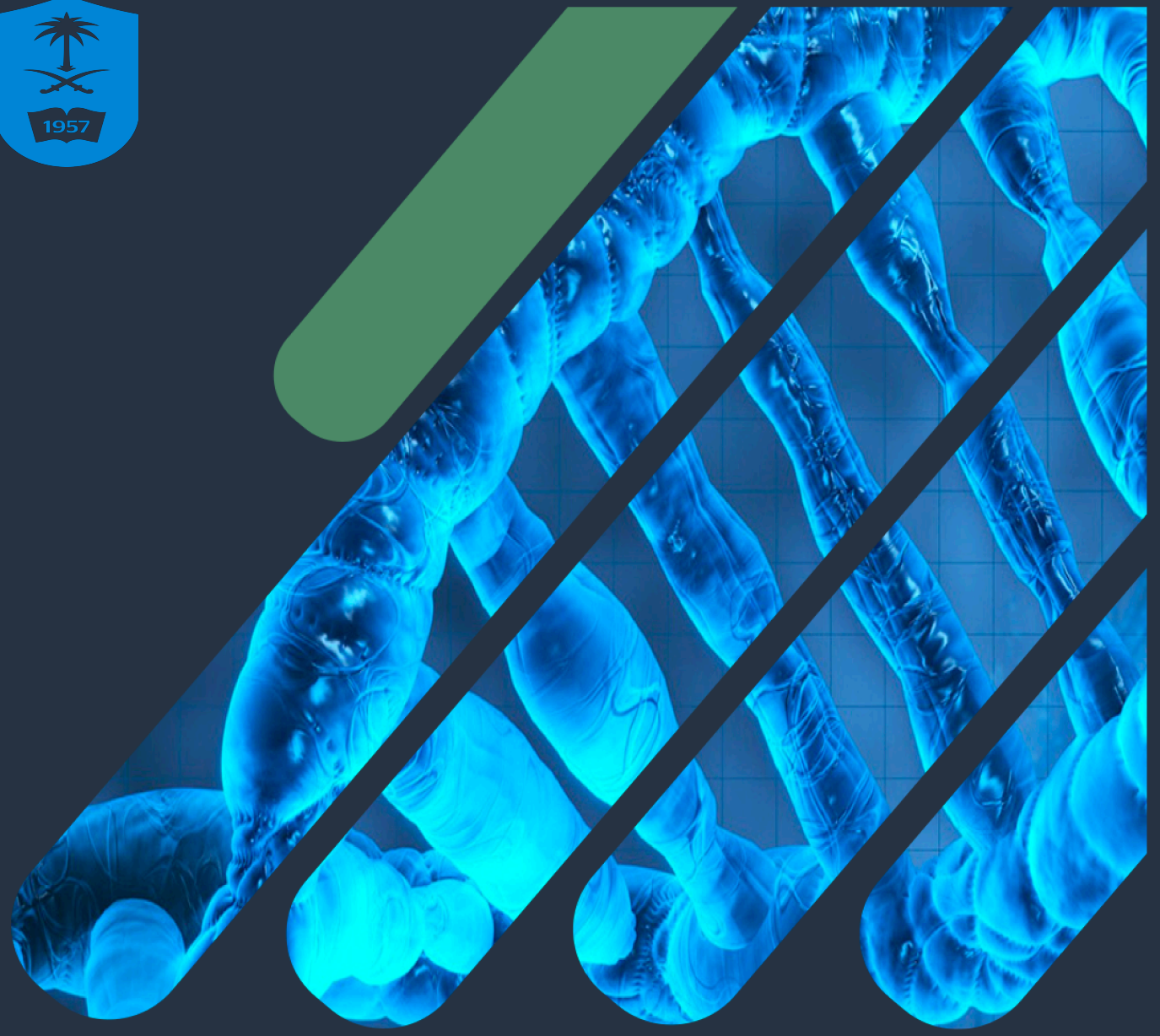
Biochemistry

MI Biomarkers



You never lose.
Either you win
or you learn ..

Revised by
شوق الأحمري & طراد الوكيل

- Important.
- Extra Information.
- Doctors slides.
- Doctors notes.

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OBJECTIVES:

By the end of this lecture the students will be able to:

- Describe the general sequence of events of myocardial infarction (MI)
- List the criteria for diagnosis of MI
- Discuss the features of an ideal MI marker
- Understand the significance of changes in plasma marker levels over time
- Identify the properties and diagnostic value of cardiac troponins, Creatine kinase, h-FABP and BNP
- Know about markers with potential clinical use

Pathological information that Dr.Sumbul recalled:

Irreversible Ischemia leads to infraction
Infraction is the necrosis (cell death) because of the ischemia.
If it's with cardiac cells we call it myocardial infraction.
The underline pathology of myocardial infraction:
Atherosclerosis
Atheroma blocking the artery.
Blood clot formation if it's big enough, it is going to completely acclot the artery which leads to ischemia.
The blood will not reach the the region it will supply that part of the artery is suppling to and that will lead to the death of those cells

MI Steps

Occlusion of the coronary arteries

Restricted blood supply to the heart tissue

Ischemia Because O2 supply is restricted.

Damage to the heart tissue

Infarction

Release of enzymes and proteins into the blood

And these become the target to select the biomarker

Criteria of diagnosing MI

- This criteria is recommended by the European Society of Cardiology and American College of Cardiology .
- Requires presence of at least two of the following characteristics:
  1. Typical heart attack symptoms
  2. Characteristic rise and fall pattern of a cardiac marker in plasma
     - Rise and gradual fall of cardiac troponins
     - More rapid rise and fall of CK-MB
  3. Typical ECG pattern

Which means the patient history such as: chest pain, shortness of breath, tightness of the jaws.

Sometimes we see it and sometimes we don't

Myocardial infarction can be present with:
- ST elevation -> STEMI
- without ST elevation -> NSTEMI (non-ST elevation myocardial infarction)

CASE 12.1

A 66-year-old man had experienced central chest pain on exertion for some months, but in the afternoon of the day prior to admission he had had a particularly severe episode of the pain, which came on without any exertion and lasted for about an hour. On admission there were no abnormalities on examination and the ECG was normal. The troponin was clearly detectable.

Comment on these results. Has he suffered a myocardial infarction?

Comments: He has an elevated troponin plus a typical history. This is sufficient to diagnose a myocardial infarction by the most recent definition, even in the absence of ECG changes.

1. Typical heart attack symptoms

2. Characteristic Pattern of a cardiac biomarker

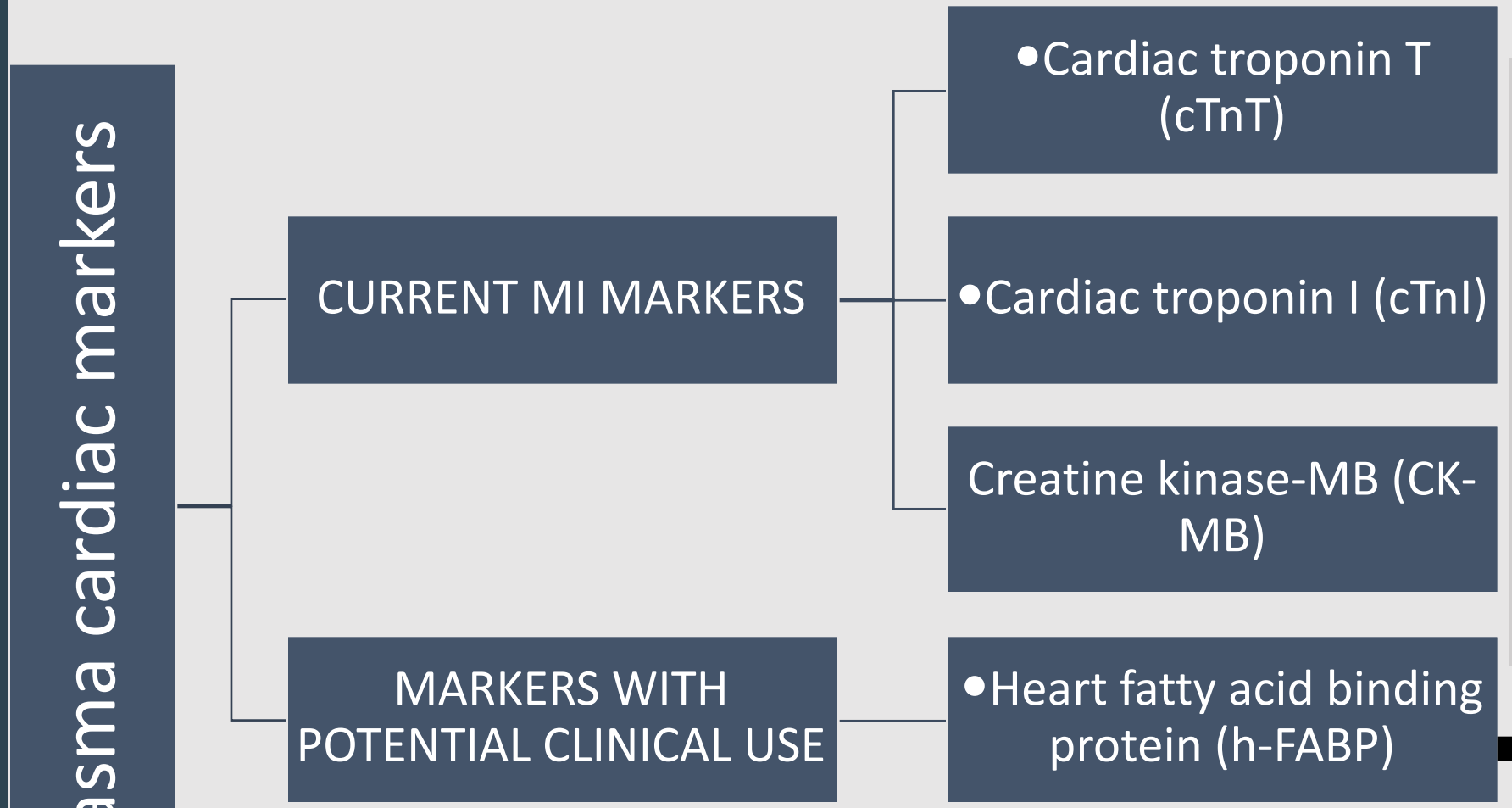
So we have 2 of the 3

Features of an ideal marker

What makes some markers better than others that they have more of these features :

- High concentration in the myocardium .
- High sensitivity (detected even in low concentration at early stages of the disease) .
- High specificity (specifically detecting damage of cardiac tissue, and is absent in non-myocardial tissue injury) .
- Rapid release into plasma following myocardial injury .
- Easily measured (detectable by rapid, simple and automated assay methods) .
- Good prognostic value (strong correlation between plasma level and extent of myocardial injury) .

Plasma cardiac markers



- ***MARKERS NO LONGER USED***
  1. Aspartate Transaminase (AST)
  2. Lactate dehydrogenase (LDH)
  3. Ischemia modified albumin (IMA)
  4. Myoglobin

(for detecting heart tissue ischemia)

- If ischemia is for 20 minutes you will have cell death.
- If ischemia is short-lived like few seconds or minutes, then the changes can be reversed.
- As soon as ischemia happen Heart fatty acid binding protein are released, and you will be able to pick it in plasma within 30 minutes.

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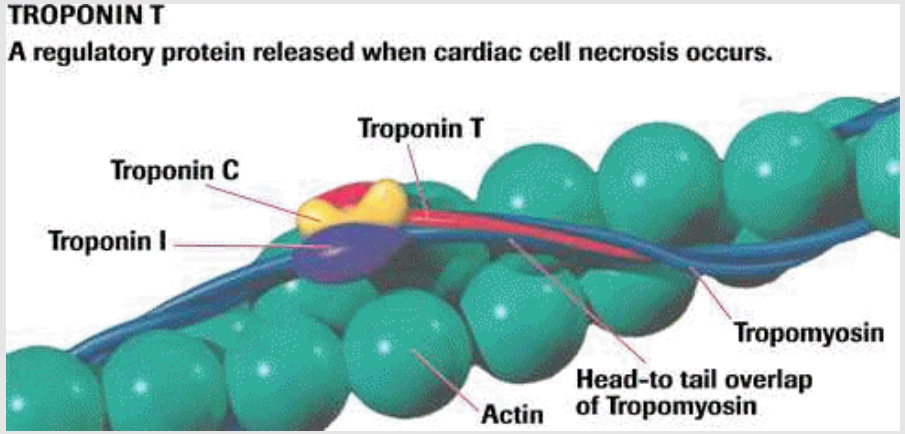
QUICK REVIEW

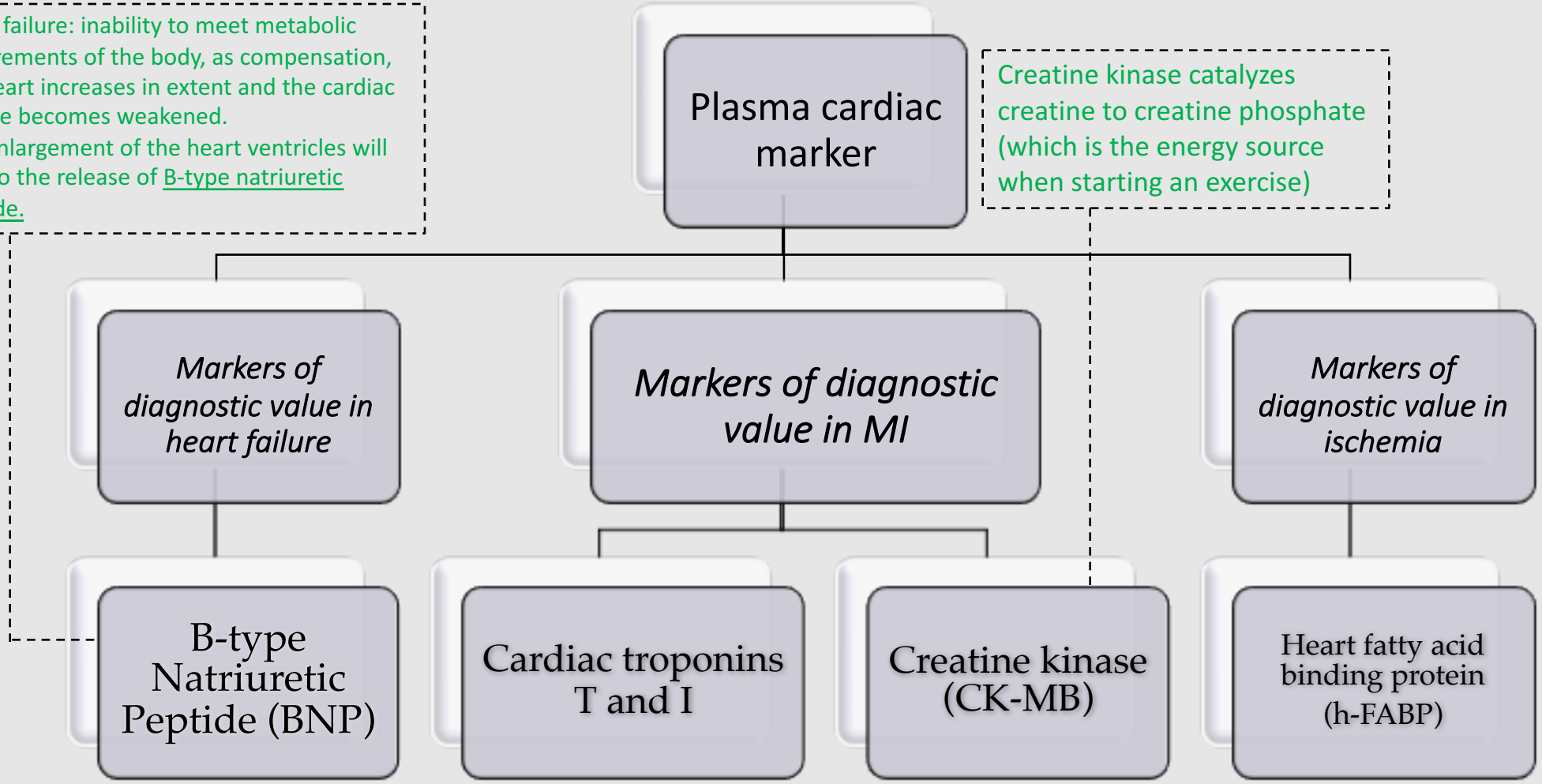
- Troponin is formed of 3 subunits:
- T: binds to tropomyosin.
- C: binds to Ca.
- I: inhibitory protein, masking the active site (where the myosin has to come and bind when the active site is not inhibited)
- When the T subunit binds to tropomyosin, they form troponin-tropomyosin complex. You have actin filament and myosin filament, for contraction to happen actin and myosin must make a cross bridge, only then the contraction will happen.
- When cardiac troponin C binds to Ca it causes conformational change in the cardiac troponin I which gets removed from the site of the actin protein.



Plasma cardiac markers

Heart failure: inability to meet metabolic requirements of the body, as compensation, the heart increases in extent and the cardiac muscle becomes weakened.
The enlargement of the heart ventricles will lead to the release of B-type natriuretic peptide.

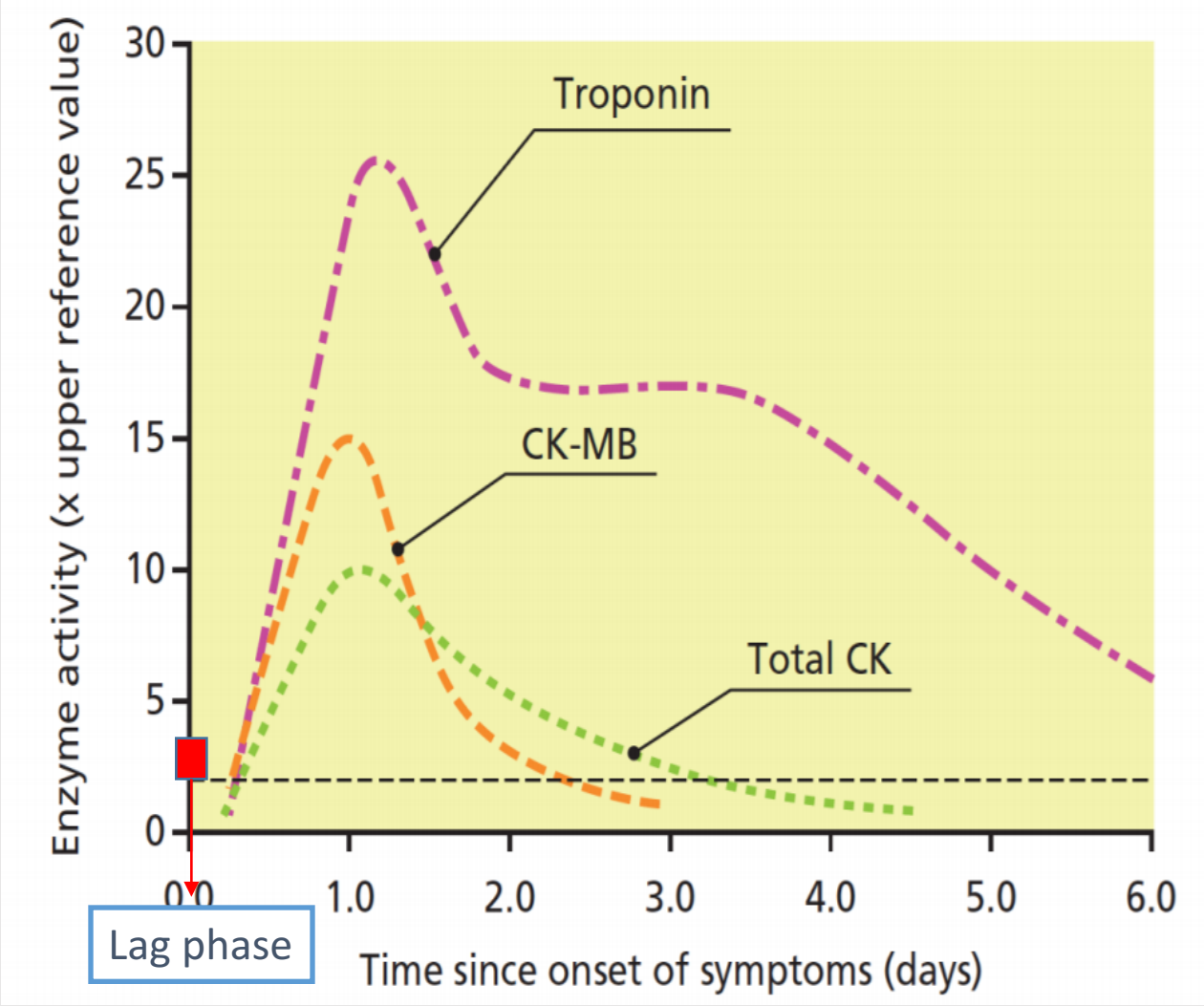
Creatine kinase catalyzes creatine to creatine phosphate (which is the energy source when starting an exercise)



- Troponins are present in skeletal muscle and the cardiac muscle.
- The cardiac troponins are structurally different where the body can make specific antibodies to them, and make specific antibodies for skeletal muscle troponins too.

Time-course of plasma enzyme changes:

- ✓ Plasma enzymes follow a pattern of activities after MI .
- ✓ The initial lag phase* lasts for about 3 hours .
- ✓ Enzymes rise rapidly to peak levels in 18-36 hours .
- ✓ The levels return to normal based on enzyme half-life .
- ✓ Rapid rise and fall indicates diagnostic value .



*Lag phase : a phase where plasma enzymes conc. are not changed yet ..

Lag Phase
الفترة ما بين حصول الضرر في النسيج والمقدرة على حساب تركيز المادة المُفرَزة في الدم

المحور الرأسي: الحد الطبيعي الأعلى للانزيم مضروب في عدد تضاعفه
يعني اقول: تضاعف التروبونين ٢٥ مرة، أو ارتفع التروبونين ٢٥ مرة ضعف المعدل الطبيعي الأعلى

Blood samples collected after MI

The types of blood samples taken depends on the time :

- ✓ Baseline (upon admission).
- ✓ Between 12 and 24 hours after the onset of symptoms.

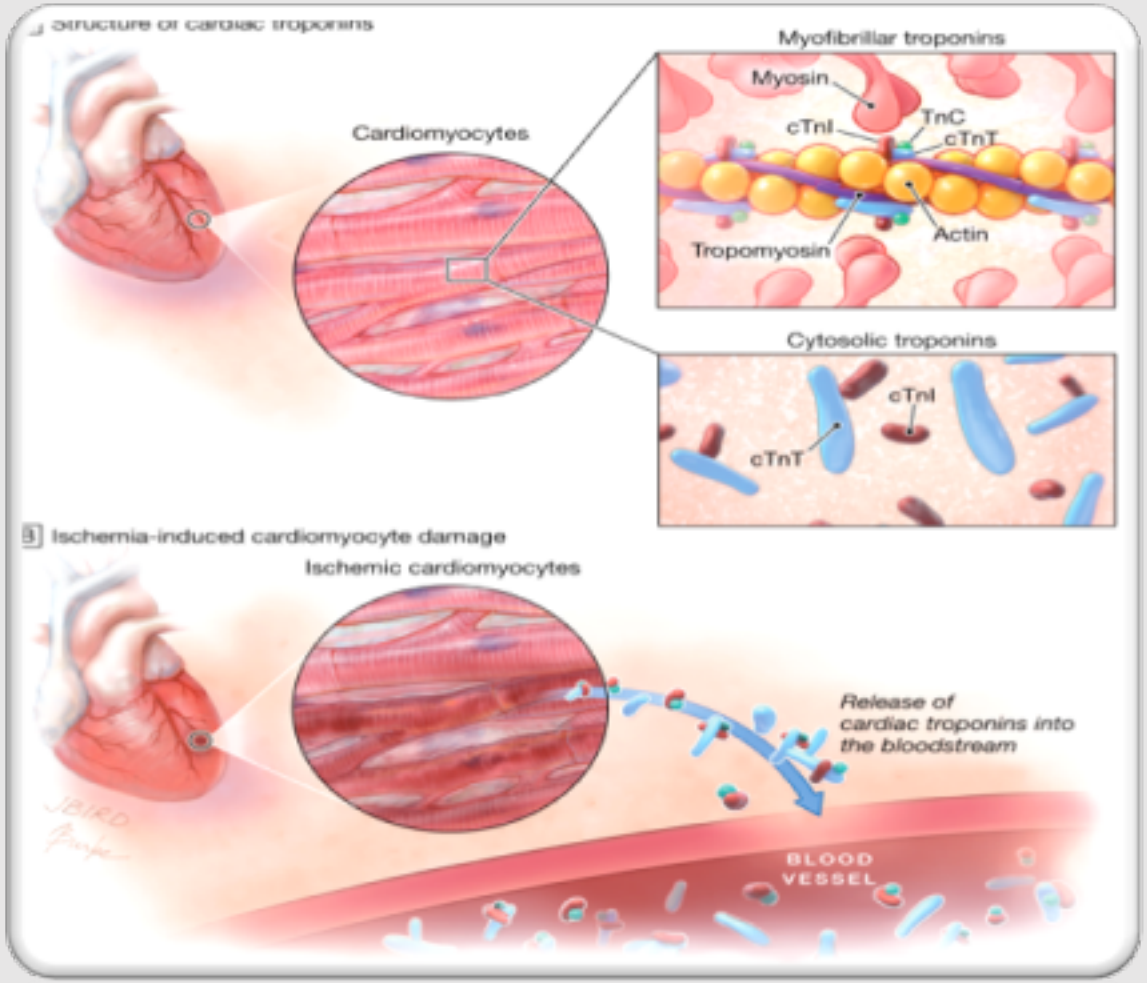
Time-course of plasma marker changes after MI

Enzyme	Abnormal activity detectable (Hours)	Peak value of abnormality (Hours)	Duration of abnormality (Days)
Troponin T , I	4 – 6	12 – 24	3 – 10
CK-MB	3 – 10	12 – 24	1,5 – 3
Total CK	5 – 12	18 – 30	2 – 5

Check the figure in the previous slide ..

Troponins

- Troponins are structural proteins in cardiac myocytes and in skeletal muscle.
- Involved in the interaction between actin and myosin fibers for muscle contraction.
- Cardiac troponins (cTn) are structurally different from muscle troponins.

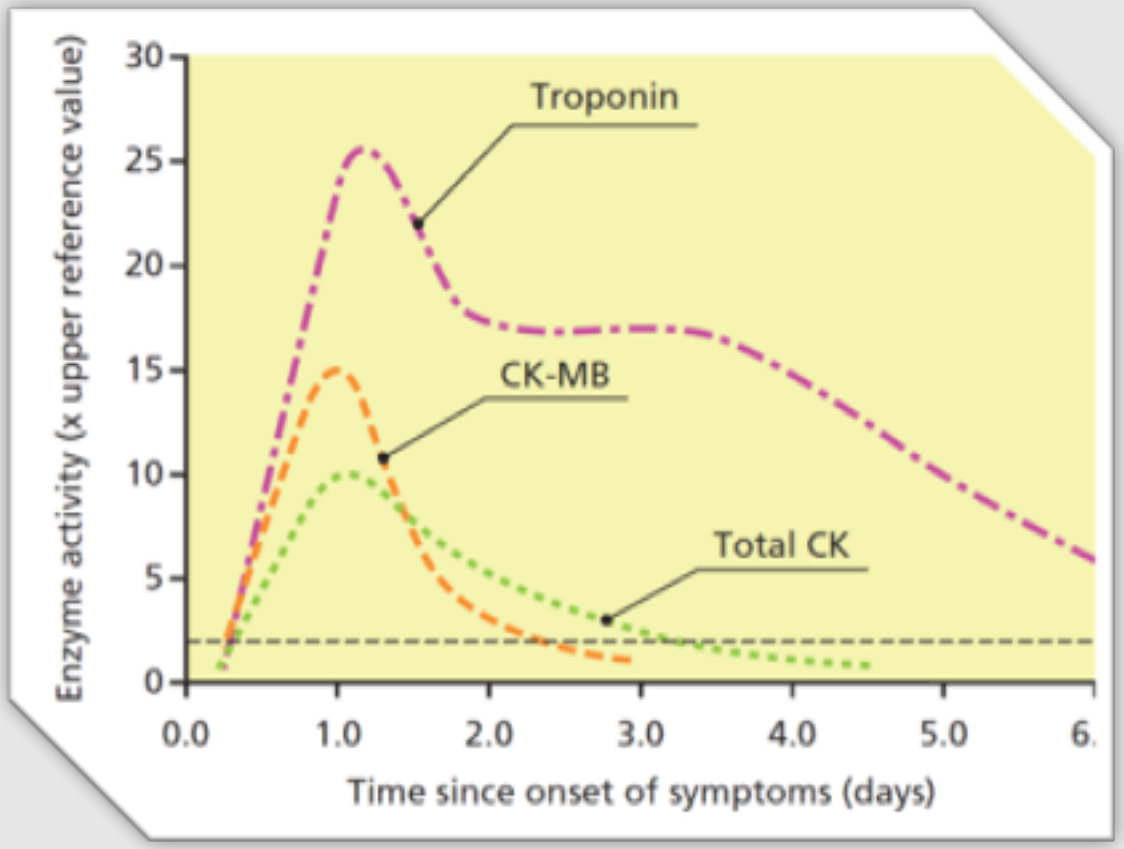


Troponins

- cTn (cardiac troponins) are mainly bound to proteins, with small amount soluble in the cytosol.
- Highly specific markers for detecting MI.
- Two main cardiac troponins (cTn):
  - **cTnI**: inhibitory protein.
  - **cTnT**: binds to tropomyosin.

Troponins

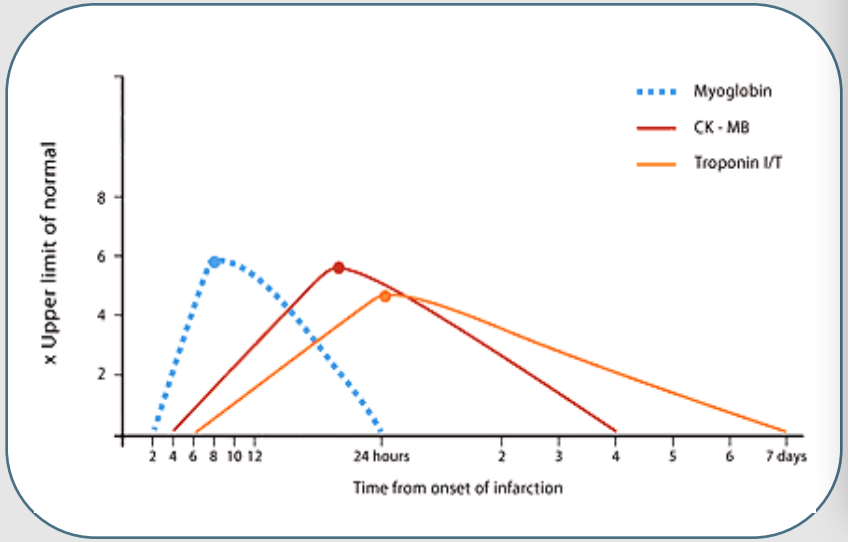
- Detectable in plasma in 4-6 h. after MI.
- Level peaks in 12-24 h.
- Remain elevated for up to 10 days.
- After MI, cytosolic troponins are released rapidly into the blood (first few hours).
- Structurally bound troponins are released later for several days.



Creatine Kinase CK

- Three main CK isoenzymes with two polypeptide chains B or M.

Creatine kinase MB are less specific than troponins; because creatine kinase MB is present at 2% in skeletal muscle too!

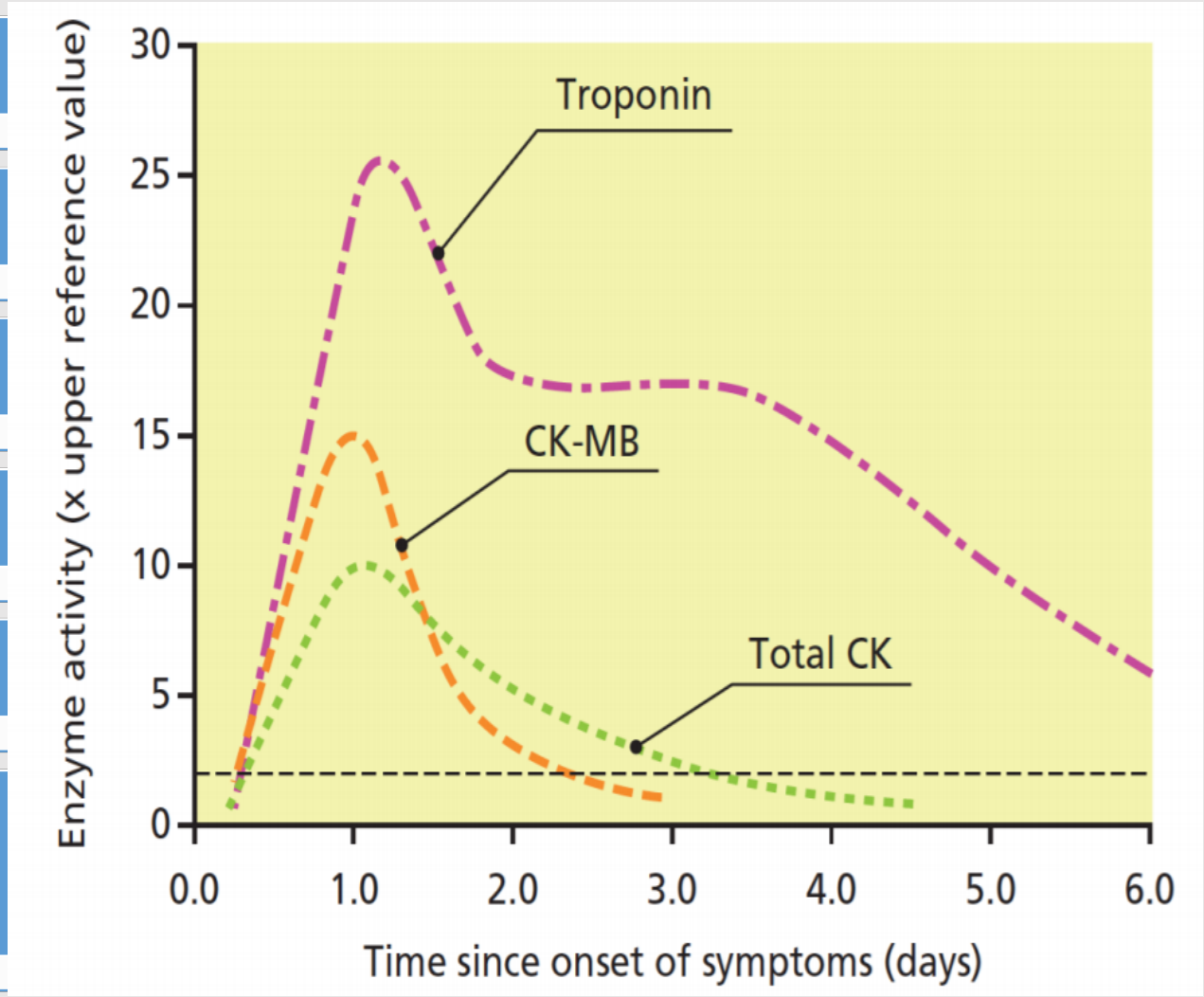


Type	Composition	Comment
Skeletal Muscle	98% CK-MM 2% CK-MB	Elevated in muscle disease
Cardiac muscle	70-80% CK-MM 20-30% CK-MB	Cardiac muscle has highest amount of CK-MB
Brain	CK-BB	
Plasma	Mainly CK-MM	

CK-MB can be found in the plasma in case of skeletal muscle injury ..

CK-MB

- More sensitive and specific for MI than Total CK
- It raises and falls transiently after MI
- Detectable in plasma in 3-10 hours
- Peaks in blood in 12-24 hours
- Returns to normal in 1.5 – 3 days
- Relative index :
  CK MB mass / Total CK x 100
  More than 5% is indicative for MI



CK-MB

Advantages:	Disadvantages:
Useful for early diagnosis of MI	Not significant if measured after 2 days of MI (delayed admission)
Useful for diagnosis of re-infarction	Not highly specific (elevated in skeletal muscle damage)

Creatine kinase MB is released to blood earlier than troponin.

It is expected for a MI patient to have recurrent MI. Because troponin can be present in blood for 10 days, then we can't tell if the patient had another MI or not! But because the CK-MB falls within 3 days, we can detect that it fell down and re-raised again which tells us that the patient had another MI.

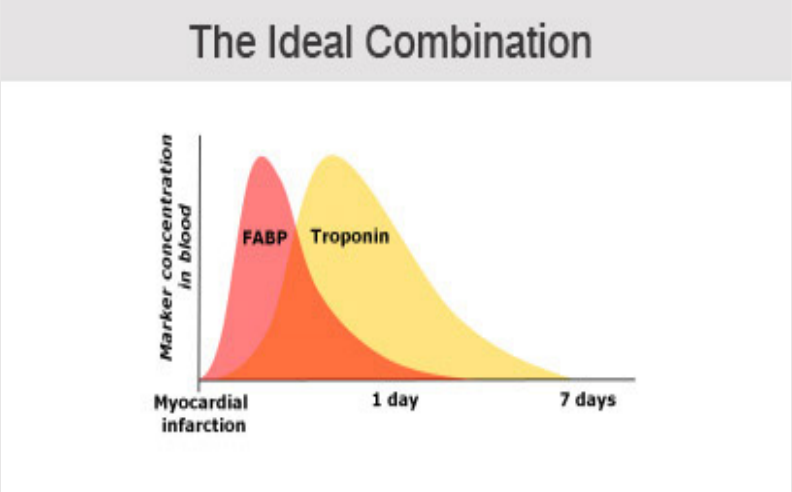
CASE 12.2

A well-trained marathon runner collapsed as he was approaching the finishing line. An ECG was normal, but CK was elevated at 9500 U/L (reference range 30–200 U/L), and the CK-MB was 14% of the total CK (normally <6%). Troponin was undetectable. Comment on these results.

Comments: The total CK is substantially elevated, and CK-MB >6% can usually be taken to mean that it is of myocardial origin. However, the normal ECG and troponin are both reassuring. In trained endurance athletes, the proportion of CK-MB in muscle increases from the normal low levels and may be as high as 10–15%. An elevated CK-MB in such individuals can no longer be taken to imply a cardiac origin for the raised CK. Extreme exercise, especially in unfit individuals, causes an elevated CK, potentially to very high levels.

Heart fatty acid binding protein (h-FABP) (Heart tissue ischemia marker)

- A cytosolic protein involved in fatty acid transport and metabolism .
- ✓ A promising marker to be used in combination with troponins .
- Higher amounts in myocardium than in brain, kidney and skeletal muscle
- ✓ Appears in plasma as early as 30 min. after acute ischemia
- Peaks in blood in 6-8 h. (Due to rapid renal clearance of this marker)
- ✓ Returns to normal levels in 24-30 h.



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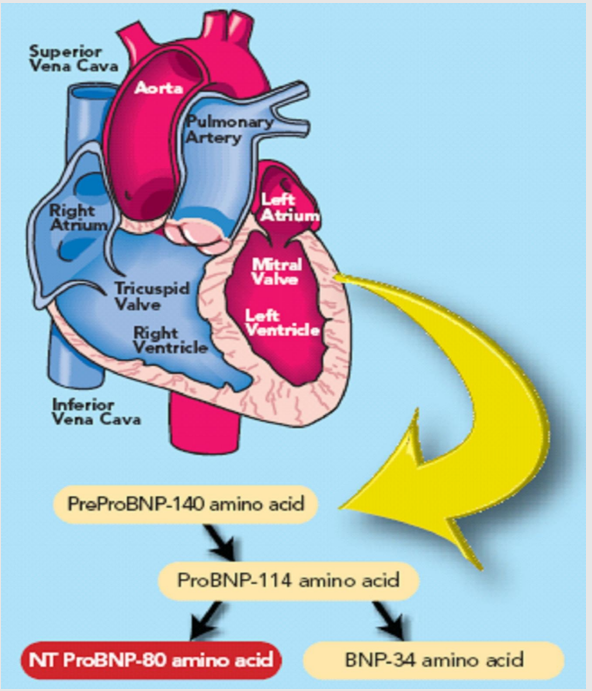
B-type natriuretic peptide (BNP) (Heart failure marker)

- A peptide produced by the ventricles of the heart in response to:

  Myocardial stretching and ventricular dysfunction after MI

- Causes : vasodilation, sodium and water excretion and reduces blood pressure .
- A marker for detecting Congestive heart failure .
- Its serum levels are high in some pulmonary diseases .
- But in heart failure its levels are markedly high .
- An important marker for differential diagnosis of pulmonary diseases and congestive heart failure .

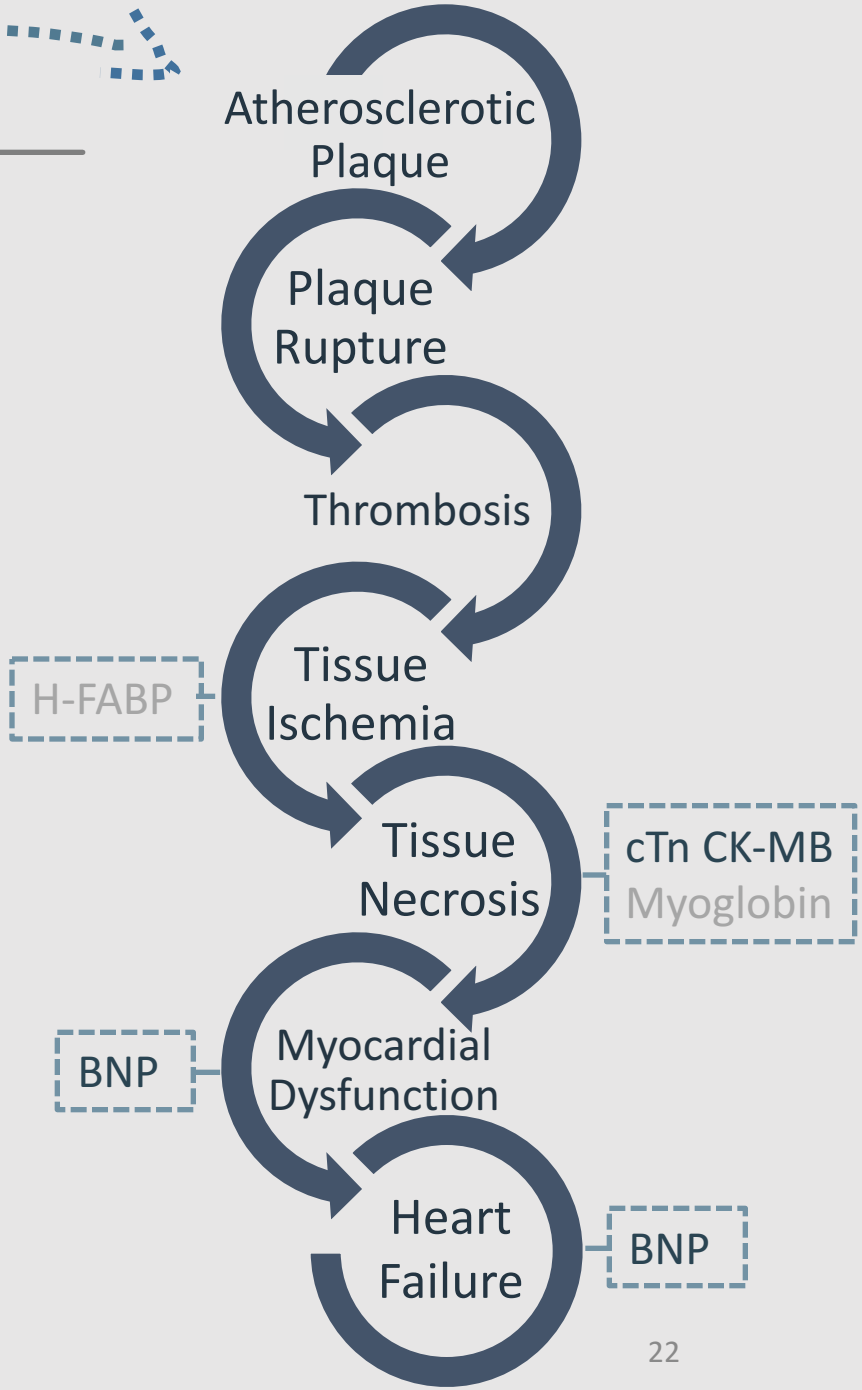


Pathogenesis of MI

Diagnosis of MI

- Typical heart attack symptoms
- Typical ECG pattern(changes)
- Typical rise and fall pattern of a cardiac marker in plasma
  - More rapid rise and fall of CK-MB
  - Typical rise and gradual fall of cardiac troponins

NOTE: Requires presence of at least two of these characteristics



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Quiz

SAQ

https://www.onlineexambuilder.com/mi-biomarkers-saq-s/exam-144724

MCQ's

https://www.onlineexambuilder.com/mi-biomarkers/exam-144722

Helpful video

https://www.youtube.com/watch?v=kO8-RPIkuLE

See you next block ☺

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TEAM MEMBERS

مهند الزهراني

طلال الطخيم

عبدالعزيز الصومالي

سعود الشنيفي

صالح التويجري

محمد العسيري

TEAM LEADERS

محمد المطلق

رانيا العيسى

بشرى قوقندي

زينة الكاف

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THANK YOU

PLEASE CONTACT US IF YOU HAVE ANY ISSUE

- Review the notes

- https://www.youtube.com/watch?v=kO8-RPIkuLE

- Lippincott's Illustrated Reviews: Biochemistry, 6th E

- @436Biochemteam

- Biochemistryteam436@gmail.com

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