Biochemical Markers of Myocardial Infarction

Cardiovascular System Block

Objectives

By the end of this lecture, the First Year 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

Overview

- Myocardial infarction (MI)
- Criteria for diagnosis of MI
- Case example for MI
- Features of an ideal MI marker
- Time-course of plasma enzyme changes
- Cardiac troponins I and T
- Creatine kinase (CK-MB)
- Heart fatty acid binding protein (h-FABP)
- B-type natriuretic peptide (BNP)

Myocardial infarction (MI)

Occlusion of coronary arteries

↓

Restricted blood supply (oxygen) to heart tissue (ischemia)

↓

Damage to heart tissue (infarction)

↓

Release of enzymes and other proteins into the blood (markers)

Criteria for diagnosis of MI

- 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

Reference: Alpert JS, Thygesen K, Antman E, Bassand JP. *J Am Coll Cardiol*. 2000, 36(3):959.

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.

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1. Typical heart attack symptoms

2. Characteristic Pattern of a cardiac biomarker

Features of an ideal cardiac marker

- 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)

Features of an ideal cardiac marker

- Rapid release into plasma following myocardial injury
- Good prognostic value (strong correlation between plasma level and extent of myocardial injury)
- Easily measured (detectable by rapid, simple and automated assay methods)

Plasma cardiac markers

- CURRENT MI MARKERS
  - Cardiac troponin T (cTnT)
  - Cardiac troponin I (cTnI)
  - Creatine kinase-MB (CK-MB)

- MARKERS WITH POTENTIAL CLINICAL USE
  - Heart fatty acid binding protein (h-FABP)

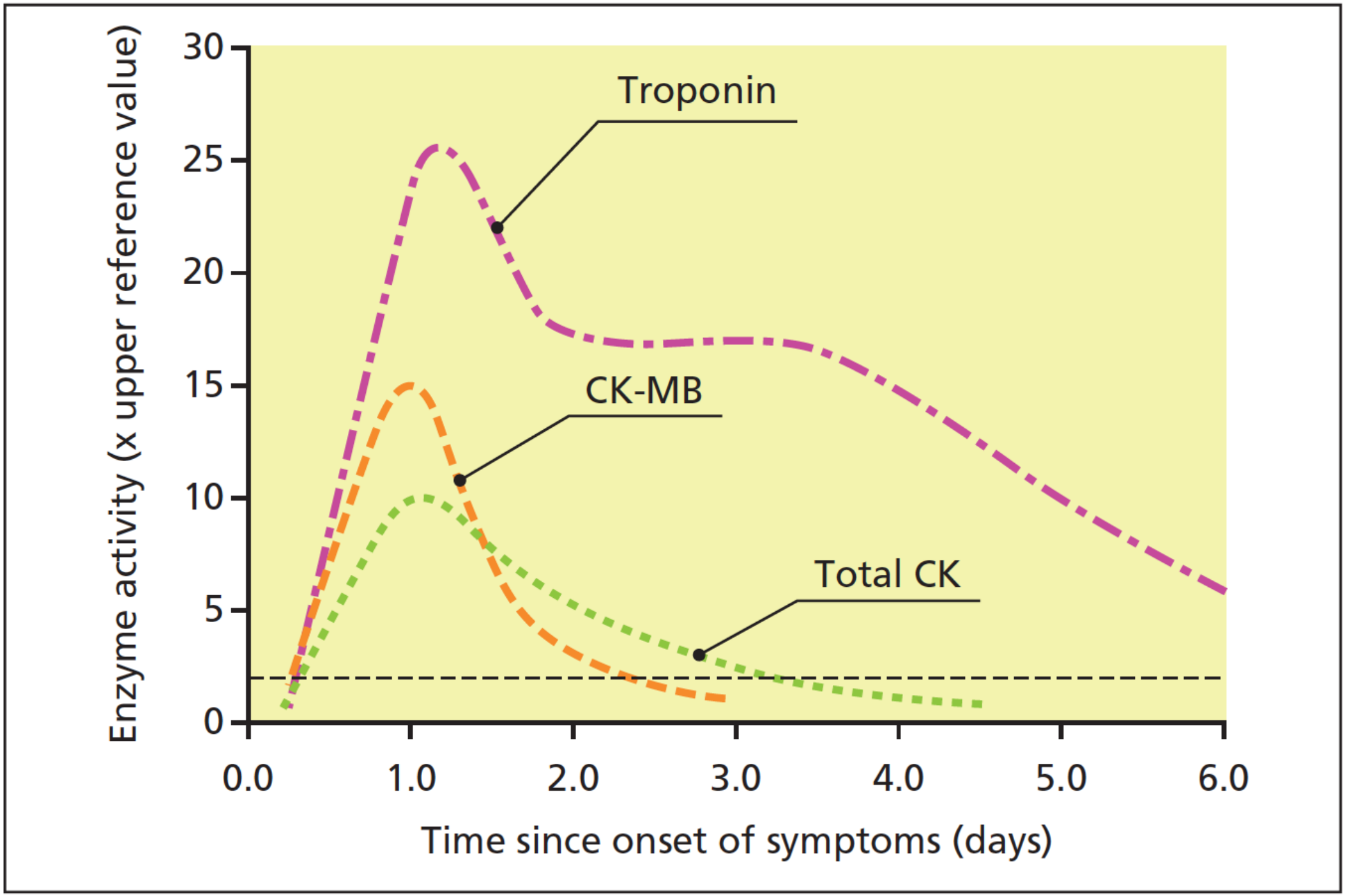
  (for detecting heart tissue ischemia)

- MARKERS NO LONGER USED
  - Aspartate Transaminase (AST)
  - Lactate dehydrogenase (LDH)
  - Ischemia modified albumin (IMA)
  - Myoglobin

- Markers of diagnostic value in MI:
  - Cardiac troponins T and I
  - Creatine kinase (CK-MB)
- Markers of diagnostic value in tissue ischemia:
  - Heart fatty acid binding protein (h-FABP)
- Markers of diagnostic value in heart failure:
  - B-type natriuretic peptide (BNP)

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


Enzyme activity (x upper reference value)
30
25
20
15
10
5
0
Troponin
CK-MB
Total CK
0.0
1.0
2.0
3.0
4.0
5.0
6.0
Time since onset of symptoms (days)

- Blood samples collected after MI:
  - Baseline (upon admission)
  - Between 12 and 24 hours after the onset of symptoms

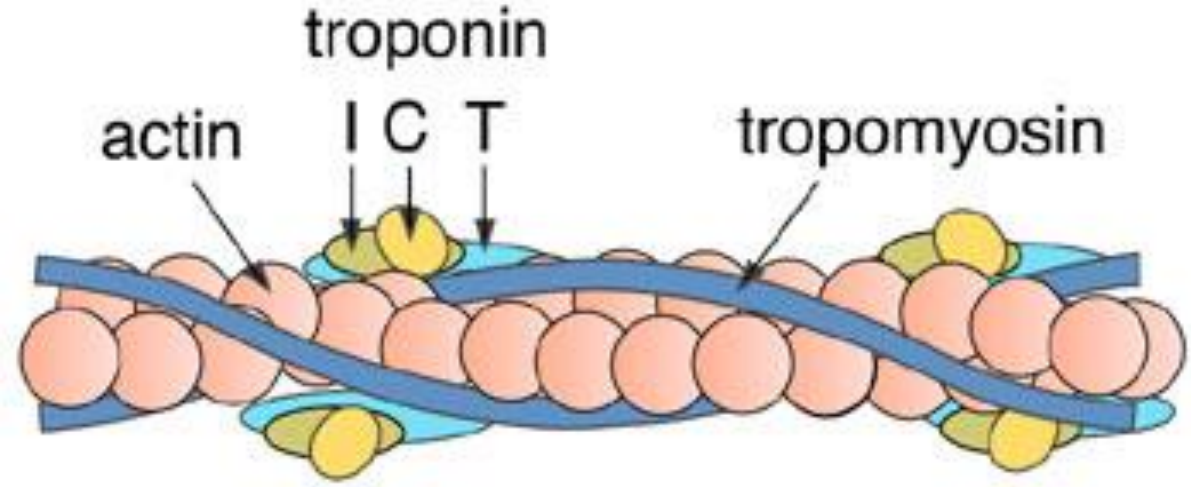
Time-course of plasma marker changes after MI

Table 12.1 Time-course of plasma biochemical marker elevation after myocardial infarction.

Enzyme	Abnormal activity detectable (h)	Peak value of abnormality (h)	Duration of abnormality (days)
Troponin T or I	4–6	12–24	3–10
CK-MB isoenzyme	3–10	12–24	1.5–3
Total CK	5–12	18–30	2–5

Troponins

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

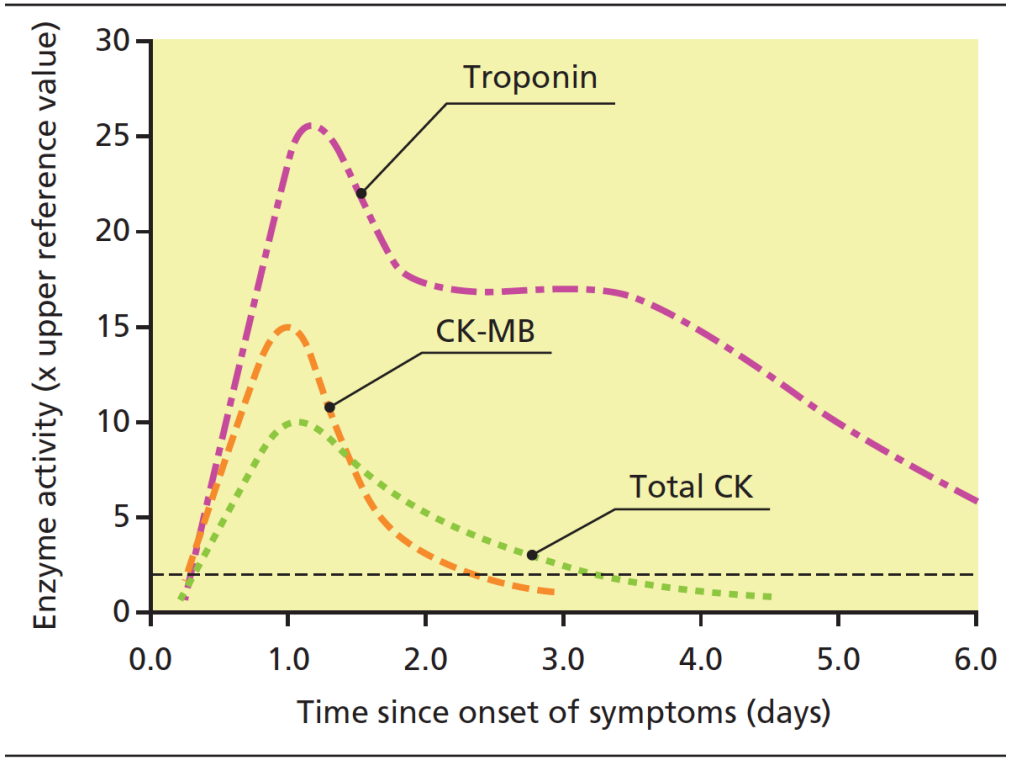


Troponins

- cTn 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



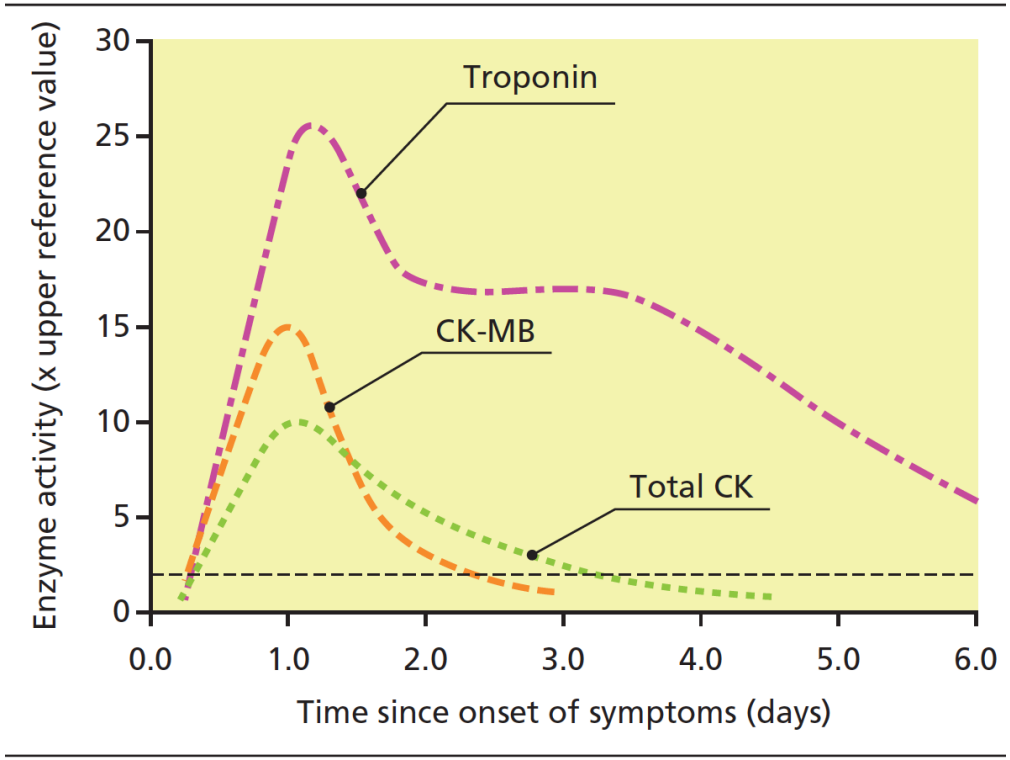
Creatine kinase (CK)

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

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

- CK-MB is more sensitive and specific for MI than total CK
- It rises and falls transiently after MI
- Detectable in plasma in 3-10 h. after MI
- Peaks in blood in 12–24 h.
- 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:

- Useful for early diagnosis of MI
- Useful for diagnosis of re-infarction

Disadvantages:

- Not significant if measured after 2 days of MI (delayed admission)
- Not highly specific (elevated in skeletal muscle damage)

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.

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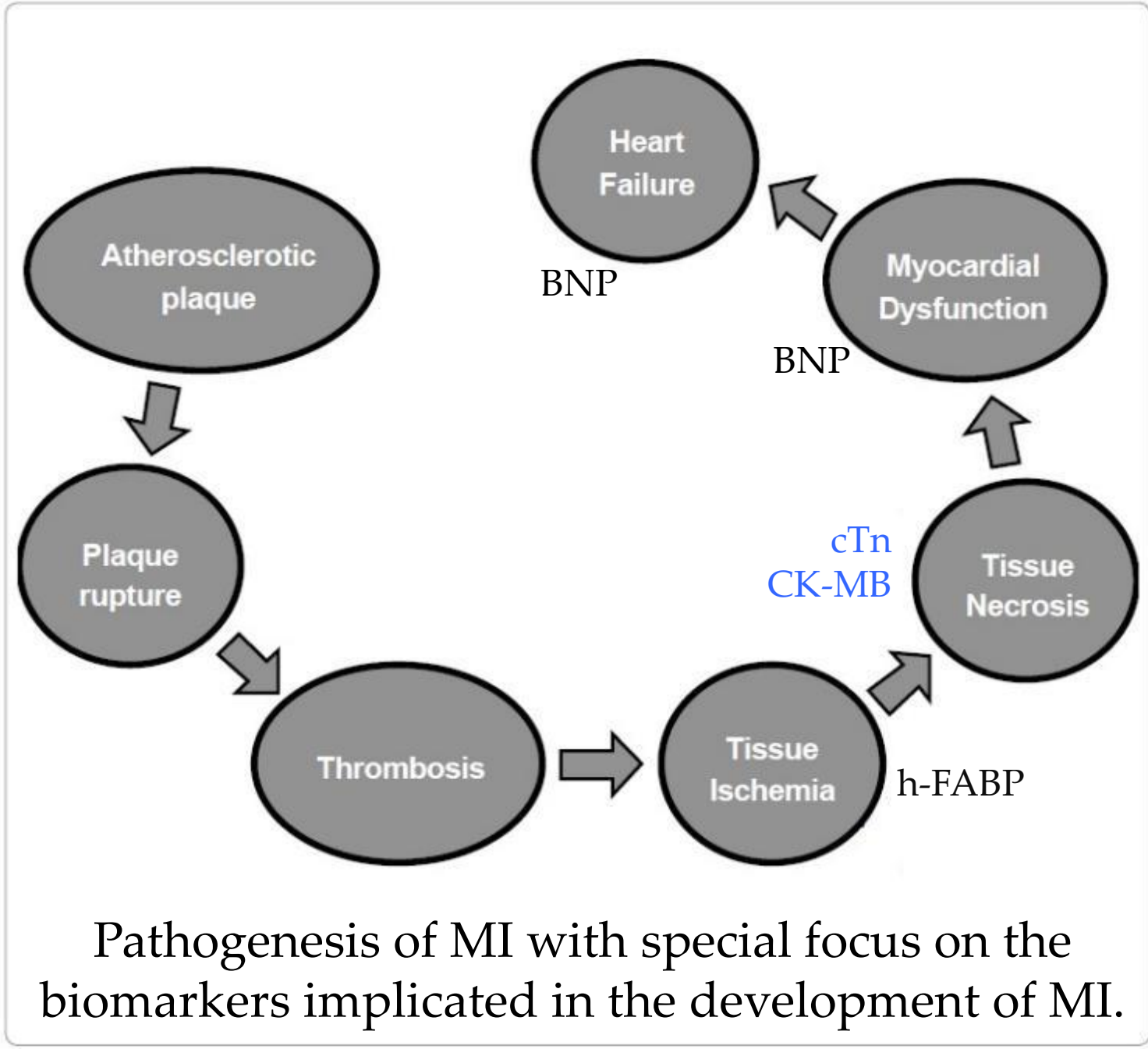
Heart fatty acid binding protein (h-FABP) (Heart tissue ischemia marker)

- 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.
- Returns to normal levels in 24-30 h.

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 with special focus on the biomarkers implicated in the development of MI.

Take home message

cTn

- Currently the most definitive markers and are replacing CK-MB
- Highly specific to heart muscle damage
- They remain elevated in plasma longer than CK-MB
- They have higher sensitivity and specificity than CK-MB

CK-MB

- Its main advantage is for detecting re-infarction

h-FABP

- An early marker for detecting acute ischemia prior to necrosis

BNP

- A cardiac marker that can be used for differential diagnosis of pulmonary diseases and heart failure

References

- Lecture Notes on Clinical Biochemistry 9th Edition, Chapter 12, pp. 160-164, A.F. Smith, Blackwell Publishing, UK.

- Sharma, N. and Ahmad, M.I. Biomarkers in acute myocardial infarction. *J. Clin. Exp. Cardiol*. 2012, 3: 11-18.