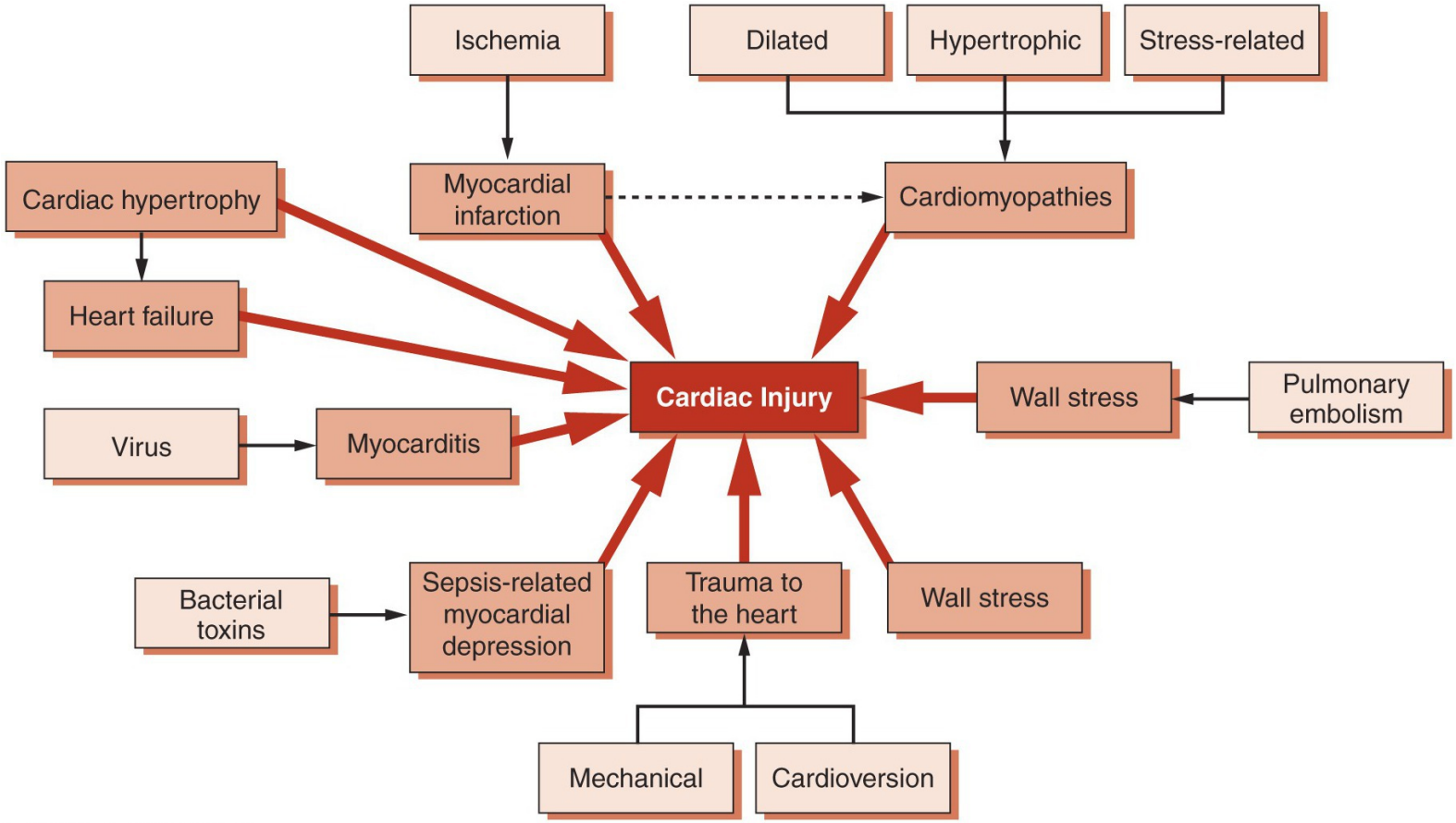
Wolters Kluwer Health | Lippincott Williams & Wilkins

Chapter 26: Laboratory Markers of Cardiac Damage and Function

By Michael Durando, Brian C. Jensen, Monte S. Willis

Sources of Cardiac Injury



Cardiovascular diseases (CVD)

- CVD commonly occurs in the general population and affects the majority of people older than 60 years
- CVDs includes four major types based on the location in which it occurs:
  - Coronary heart disease (CHD)
  - Cerebrovascular disease
  - Peripheral arterial disease
  - Aortic atherosclerotic disease

- CHD manifests as myocardial infarction (MI) (heart attack), angina pectoris (chest pain), heart failure, and sudden cardiac death
- CHD in which atherosclerosis and ischemia are localized to the vasculature of the heart, accounts for one-third of the total cases of CVD

Cardiac Ischemia, Angina, Heart Attack

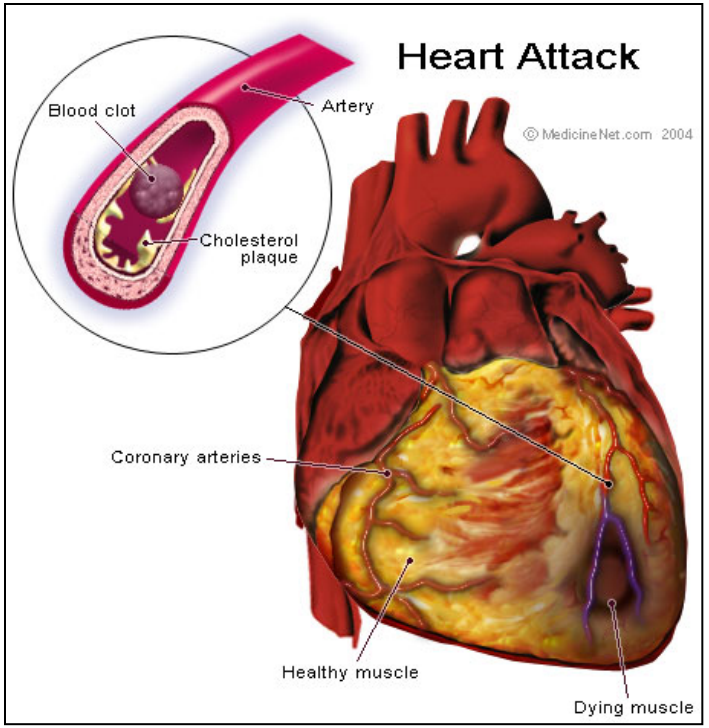
- Ischemia—lack of adequate blood supply to the heart
  - Can lead to activity-related chest pain;
    - Stable angina
    - ACS (acute coronary syndrome)
      - Can be further classified as unstable angina, or the more severe acute MI
- Cardiac biomarkers—normal in unstable angina
  - Elevated in MI
- Guidelines recommend patients be evaluated in person at an ER if chest discomfort >20 minutes at rest

Pathophysiology of cardiac ischemia, angina and MI

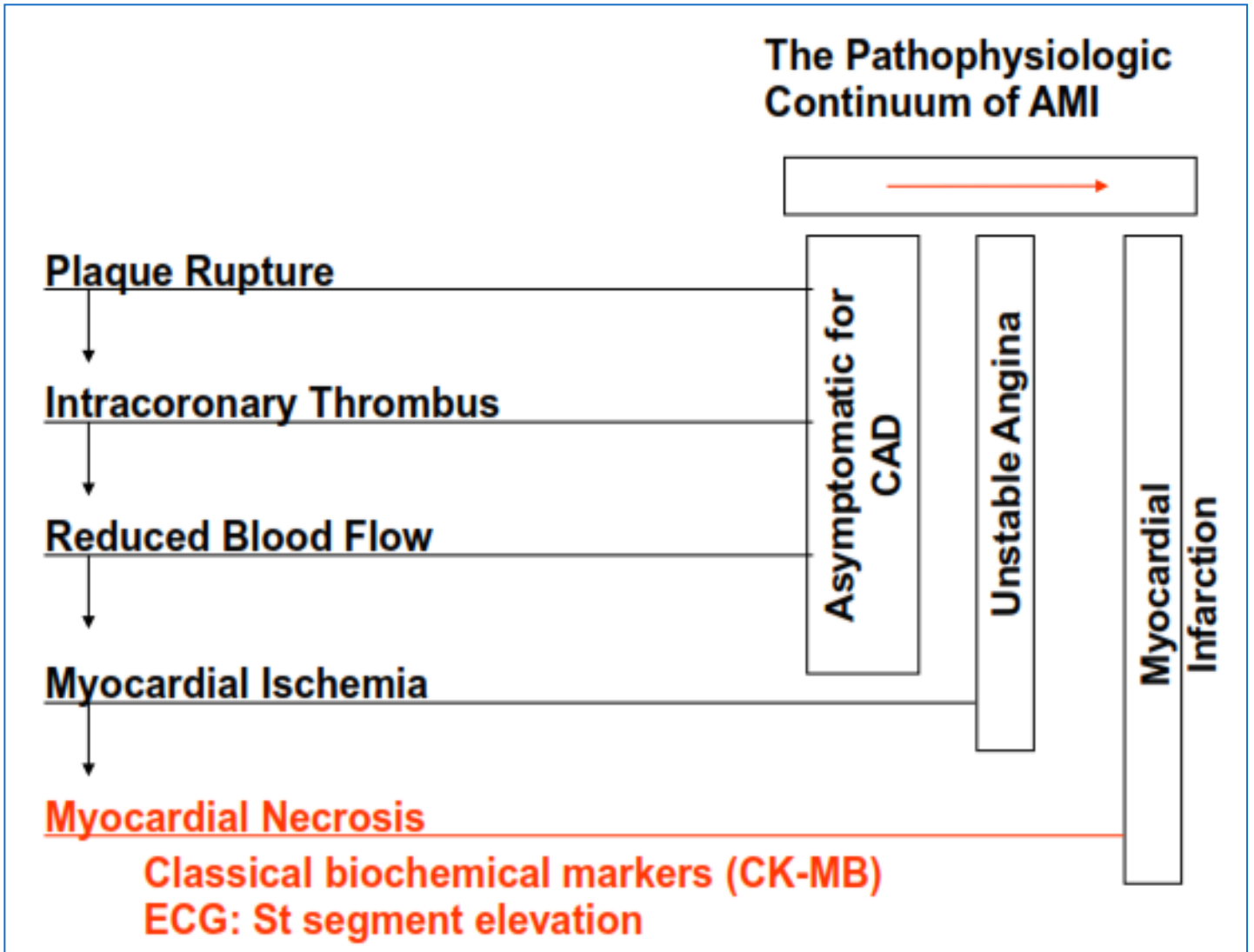
- Myocardial ischemia results from the reduction of coronary blood flow to an extent that leads to insufficiency of oxygen supply to myocardial tissue

- When this ischemia is prolonged & irreversible, myocardial cell death & necrosis occurs
  This is defined as:

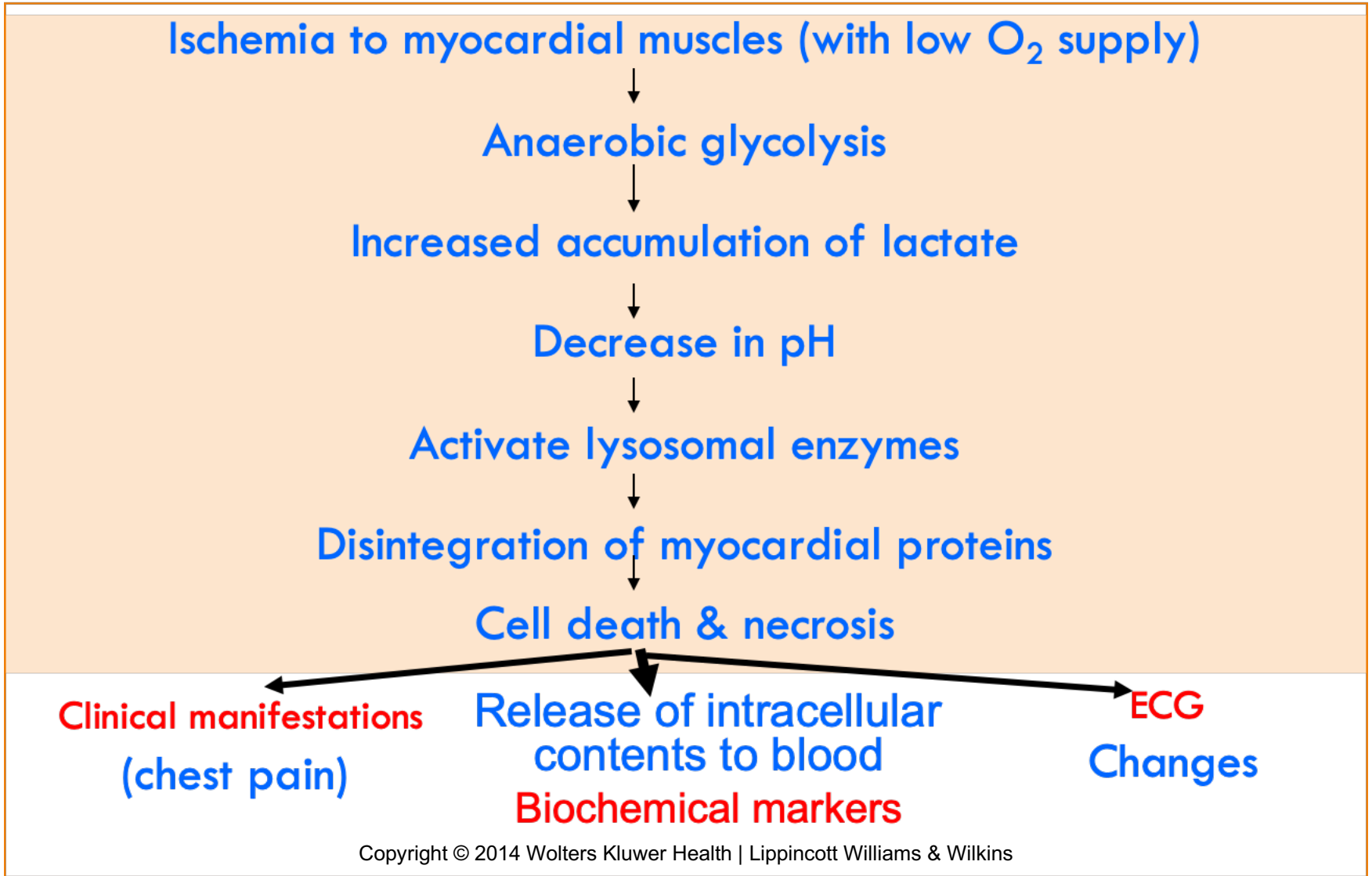
  myocardial infarction



Pathophysiology of Acute coronary syndrome (ACS)



Biochemical Changes in AMI
(mechanism of release of myocardial markers)



CASE STUDY 26-1

A 15-month-old girl with a heart murmur since birth was evaluated for repeated pulmonary infections, failure to grow, cyanosis, and mild clubbing of fingers and toes. She had been on digitalis therapy by the referring physician. The radiograph showed a moderately enlarged heart and an enlarged pulmonary artery. Pertinent laboratory data were obtained.

Total protein (6.0–8.3 g/dL)	5.4
Albumin (3.5–5.2 g/dL)	3.0
Hemoglobin (14–18 g/dL)	19.2
Hematocrit (40–54%)	59
Erythrocyte count (4.3–5.7 × 10^6/mm^3)	6.4

A cardiac catheterization was performed, and a large ventricular septal defect was found.

Questions

1. How does this congenital defect affect the body's circulation?
2. Why are the red cell measurements increased in this patient?
3. What treatment will be suggested for this patient?
4. What is this patient's prognosis?

1. *A ventricular septal defect allows blood to flow from the left ventricle to the right ventricle. This reduces the amount of blood that is pumped from the left ventricle to the systemic circulation and increases the amount of blood entering the pulmonary circulation, usually causing pulmonary hypertension. This explains this patient's enlarged pulmonary artery.*

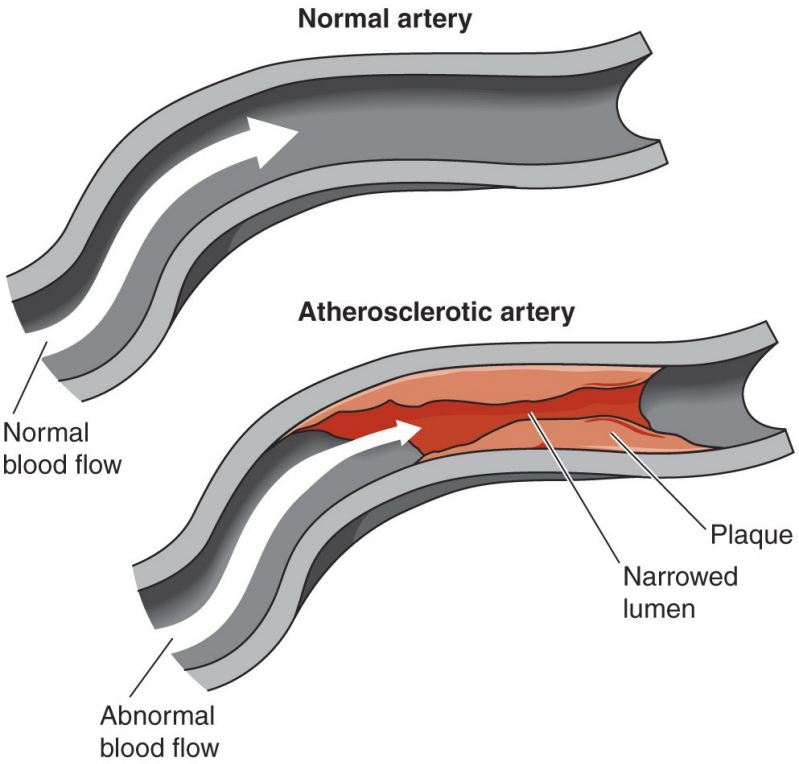
2. *A decreased flow of oxygenated blood to the body results in a compensatory response by the kidneys to increase the cellular capacity to carry oxygen by increasing the release of erythropoietin. This increases red blood cell counts, hematocrit, and hemoglobin.*

3. *Surgery to repair the septal defect*

4. *Very good, after surgery*

Pathophysiology of atherosclerosis

- Atherosclerosis is the underlying disease for MI
- Risk factors for plaque formation
  - Hyperlipemia-LDL
  - Diabetes
  - Hypertension
  - Smoking
  - Obesity



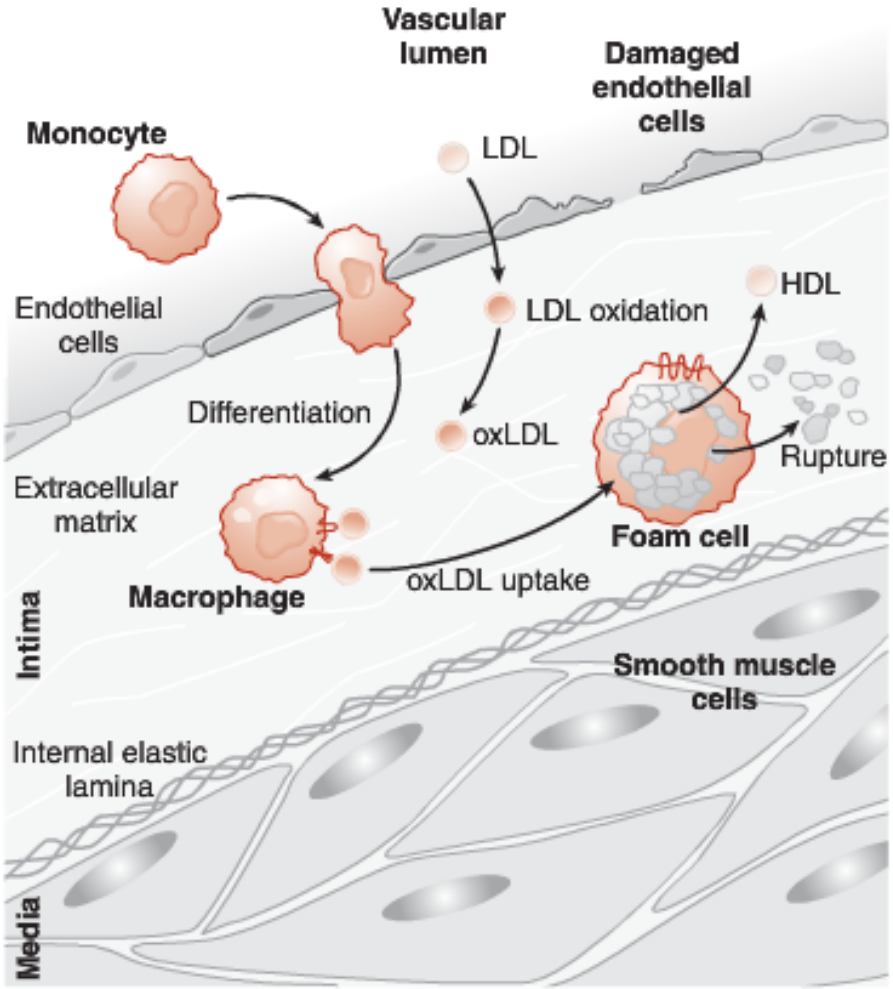


FIGURE 26-2 LDL deposition and oxidation within the vessel wall leads to monocyte recruitment and differentiation into activated macrophages that phagocytose oxidized LDL (oxLDL) to become foam cells. Foam cells release HDL and pro-inflammatory mediators and their rupture contributes to lesion progression. Adapted from Glass and Witztum.[10]

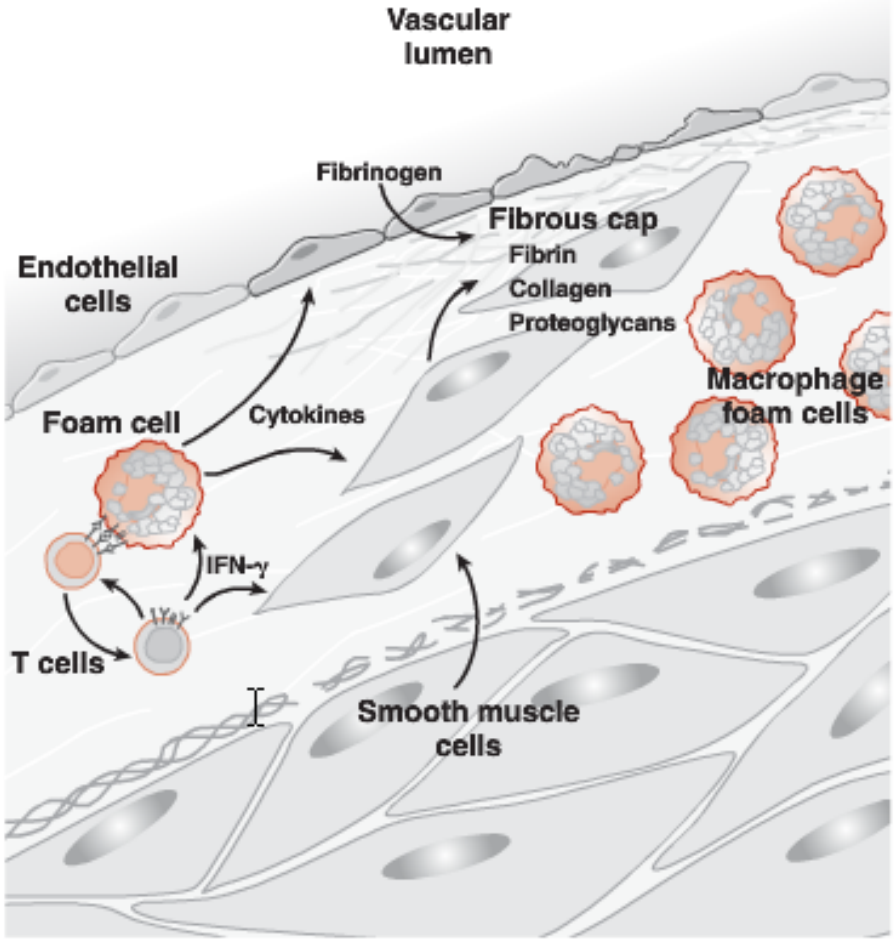


FIGURE 26-3 T cells and foam cells maintain a pro-inflammatory state that induces the migration of smooth muscle cells into the intima, where they secrete collagen, proteoglycans, and fibrin that form a fibrous cap around the atheroma. Adapted from Glass and Witztum.[10]

Markers of Cardiac Damage
Initial Markers

- Serum biomarkers have become the centerpiece of evaluation and management of patients with chest pain
- First cardiac markers included GOT/AST, lactic dehydrogenase, malic dehydrogenase
- LD was found to be more sensitive than AST; but LD could be elevated due to other conditions.
- Creatine kinase (CK); MB fraction
- Use of AST, LD, CK continued for decades

Markers of cardiac damage

- Cardiac enzymes
  - AST
  - LDH: LD-1:LD-2 ratio >0.75
  - CK Total
  - CK-MB
- Cardiac proteins
  - Myoglobin
  - Troponins

AST

- One of the first cardiac markers
- Short window of AST elevation
- High false-negative results
- Replaced by LDH

LDH

- More specific than AST
- Remains elevated for ~2 weeks post-MI
- It's elevated in other conditions like cancer and anemia
- LDH isoenzymes: LD-1 to LD-5
- LD-1 is most abundant in myocardium
- LD1:LD2 ratio >0.75 at 24-48 hrs post MI and remains elevated to 2 weeks

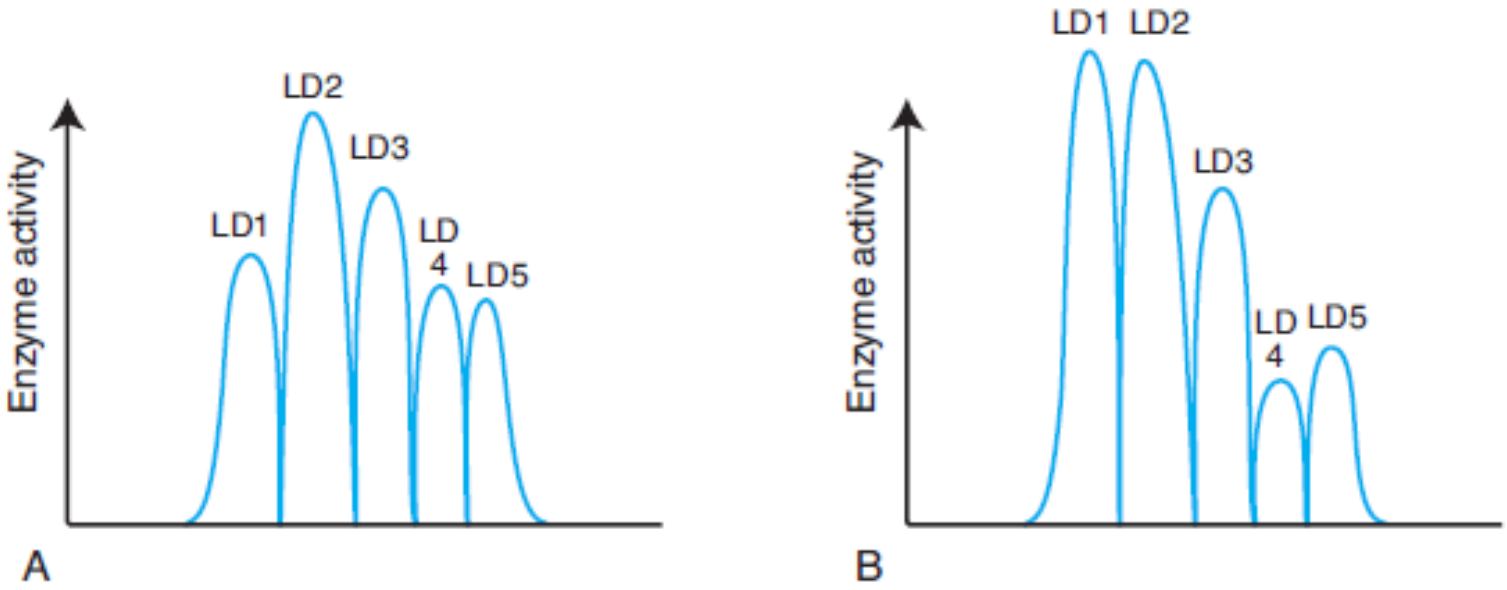


Figure 8–2. Electrophoretic separation of the LD isoenzymes in the serum of (*A*) a healthy individual and (*B*) a patient with acute myocardial infarction.

Ref: Clinical chemistry: a laboratory perspective. By Wendy Arneson & Jean Brickell, ©2007. Publisher: F.A. Davies. Chap8 / Page 275

Creatine kinase (CK)

- Total CK = CK-MM + CK-MB + CK-BB
- Like LD, it's found in nearly all cells with high levels in muscle cells especially striated muscles
- In AMI, CK exceeds normal levels within 4-6 hrs, reach a peak of 2-10X normal by 24 hrs; declines to normal by 3-4 days
- Increased CK together with increased AST and LD was used primarily for detection of MI for many years
- Elevated in other diseases like stroke, chronic alcoholism, strenuous exercise, pulmonary embolism

CK-MB (CK-2) activity

- More specific than total CK, but less specific than Troponins
- 15-30% of CK in mycardium is MB compared to 1-3% in normal striated muscles
- Appears in blood 4-6 hrs after onset of MI symptoms; peaks at 12-24 hrs; returns to normal 2-4 days post MI

CK-MB

- Advantages:
  - Useful for early diagnosis of MI
  - Useful for diagnosis of re-infarction
- Disadvantages:
  - Not useful for delayed admission (more than 2 days)
  - Not 100% specific, because it's elevated in skeletal muscle injury

CK-MB vs. CK total

- Relative index = (CK-MB mass / CK total) X 100
- More than 5% is indicative of MI

CK-MB measurement

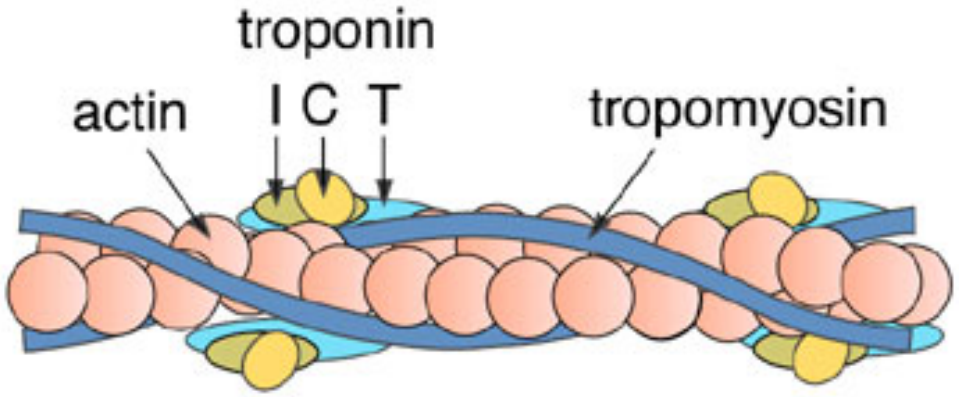
- **Principle**: Immunoinhibition allows blocking of the M isotope of the CK dimer isoenzymes & the remaining CK-B component will react in the typical CK enzyme reaction.
- **The Reaction**
- Sample is incubated in the CK-MB reagent, which includes the anti–CK-M antibody. Then CK-B is determined

Myoglobin

- Not specific for cardiac tissue (also in skeletal muscles & renal tissues)
- Appears in blood EARLIER than other markers (within 1-4 hours)
- So, it has a high sensitivity
- It has a short half-life of 9 minutes
- It returns to normal within 24 hours
- Not useful for delayed admission cases (after one day of onset of attack)

Cardiac Troponins

- Troponin is a complex of three proteins that regulate the calcium-dependent interactions of myosin heads with actin filaments during striated muscle contraction
- Troponin complex is made of 3 proteins: TnT, TnI, TnC
- TnT and TnI are used as cardiac markers
- Troponins have tissue-specific isoforms >> Cardiac Troponins are different from skeletal muscle Troponins and thus more specific for diagnosis of MI



TnI

- 100 % cardiac specific
- Has greater sensitivity for diagnosing minor damage of MI
- Appears in blood within 3-12 hours after onset of infarction
- Peaks at 12-24 hours
- Remains elevated for more than one week (stays longer)
- Useful for diagnosis of delayed admission cases
- Prognostic marker (relation between level in blood & extent of cardiac damage)
- In MI, TnI increases from 10 ng/ml to >100ng/ml
- If not available, the next best test is CK-MB

TnT vs. TnI

- Equivalent diagnostic utility for AMI and risk stratification
- TnT slightly larger than cTnI (37 vs. 24 kDa) and remains positive after AMI longer.
- Abnormal TnT found more frequently in patients with chronic renal failure than TnI due to non-ischemic myocardial damage.
- Higher myocardial tissue content
  - CK-MB: 1.4 mg/g wet weight
  - cTnI: 6.0 mg/g wet weight
  - cTnT: 10.8 mg/g wet weight

Sample used for Tn testing

- Type: plasma
- Timing:
  - on admission
  - serial (at least every one hour in a period 6-9 hours)
- should be referenced to admission & onset of pain

Cardiac Troponins (Cont'd)

- Troponins found to have tissue-specific isoforms; skeletal vs. cardiac.
- Skeletal and cardiac isoforms of TnT and TnI contain different amino acid sequences
- Possible to develop antibodies to these cardiac-specific epitopes
- Advantages over CK-MB
- cTnI or cTnT—currently preferred biomarker for myocardial necrosis (CK-MB next best)

Cardiac Biomarkers

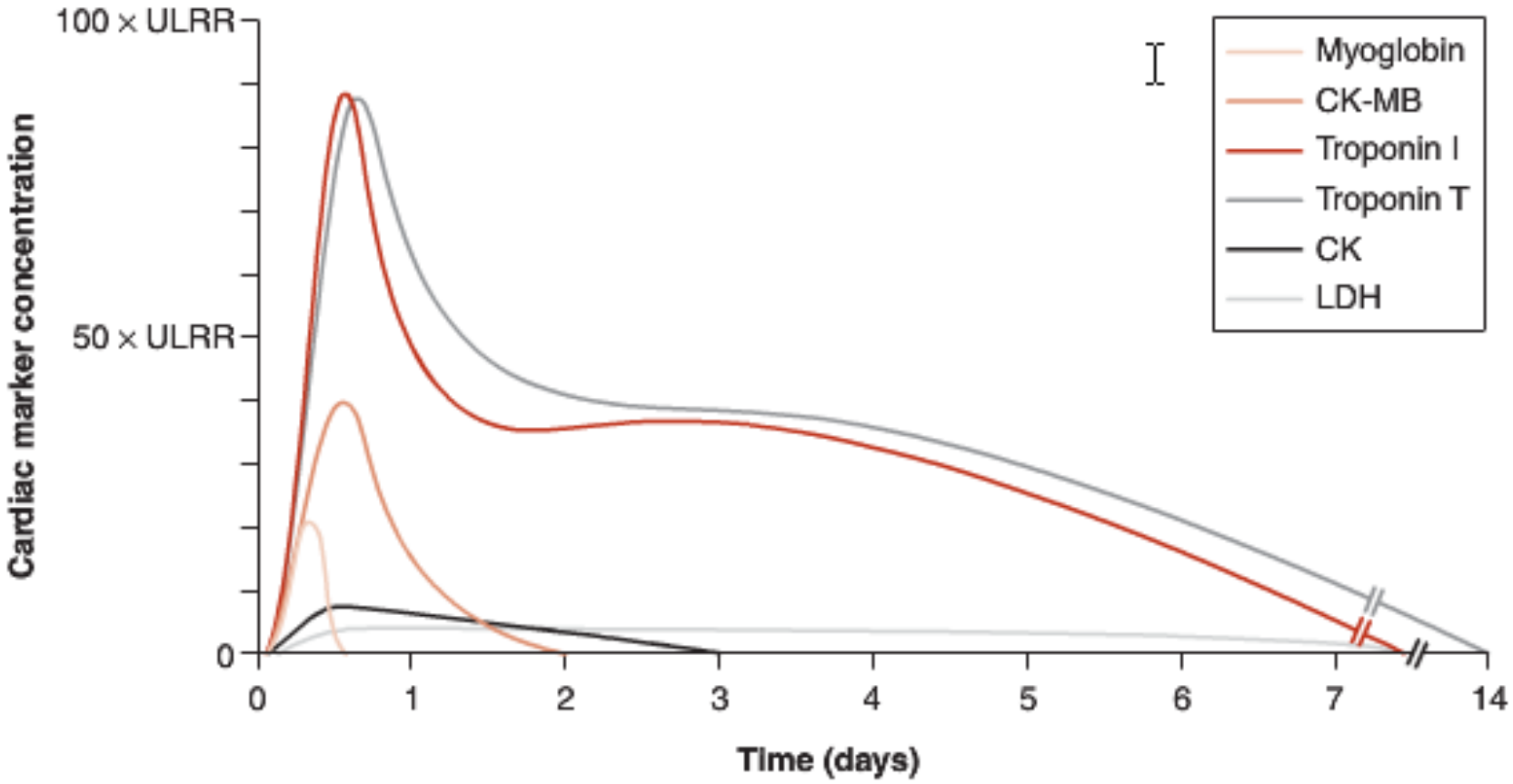


FIGURE 26-4 Temporal elevations of important markers of myocardial damage post-MI. ULRR, upper limit of reference range. Adapted from French and White.[26]

CASE STUDY 26-2

A 59-year-old woman came to the emergency department of a local hospital complaining of pain and a feeling of heaviness in her abdomen for several days. She reported no weakness, chest pain, or left arm pain. She has no chronic health problems except for seasonal allergies and slightly elevated total cholesterol.

CARDIAC ENZYMES	8:30 PM, APRIL 11	6:30 AM, APRIL 12
Total CK (54–186 U/L)	170	106
CK-MB (0–5 ng/mL)	6.3	3.8
% CK-MB (<6%)	3.7	3.6
Myoglobin (<70 µg/L)	52	41
Troponin T (0–0.1 µg/L)	0.8	2.3

Questions

1. Do the symptoms and personal history of this patient suggest acute MI?
2. Based on the preceding laboratory data, would this diagnosis be acute MI?
3. Why or why not?

Use of Cardiac Biomarkers in Heart Failure

- Heart failure—pathologic state; heart fails to adequately supply metabolic needs of the body. Typically due to decrease in pumping function
- Congestive heart failure (CHF)—most common cause of heart failure
- Monitor using:
  - B-type natriuretic peptide (BNP) or NT-proBNP
  - Troponins

Markers of CHD Risk

- C-reactive protein (CRP)
- Homocysteine

CRP

- CRP levels greater than 8.6 mg/L are released 6-12 hours following AMI
- New immunoassay methods for detecting CRP are capable of detecting as low as 0.05-0.2 mg/dL (0.5-2.0 g/L)

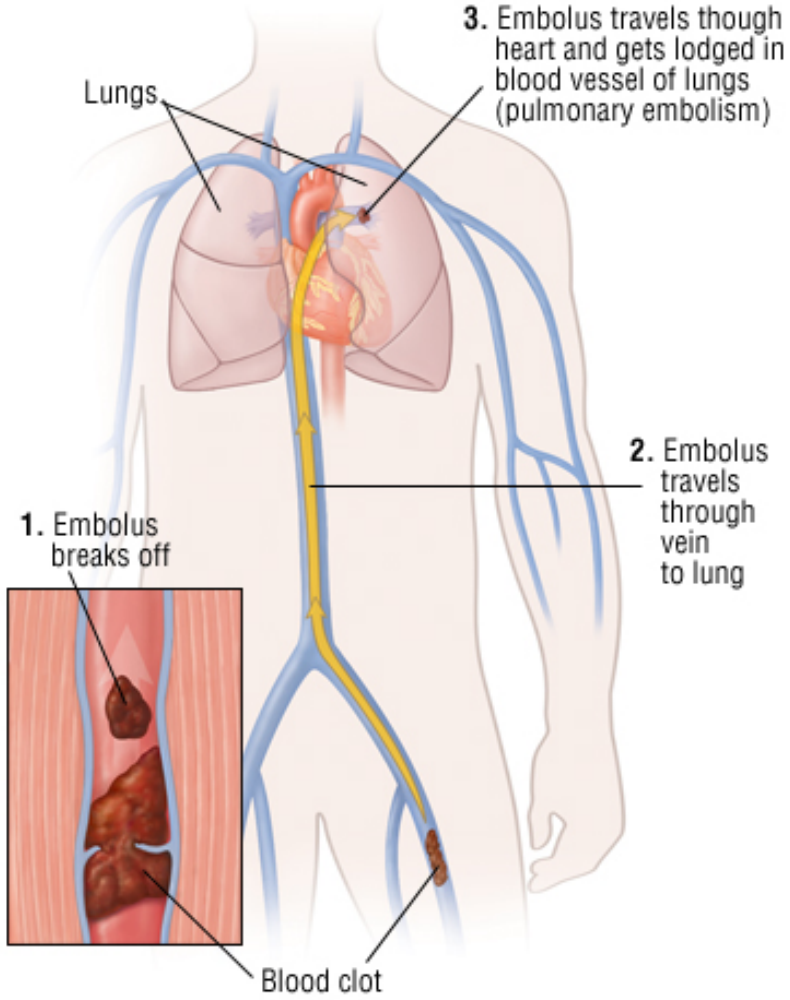
Measurement of CRP

- Detecting hsCRP by light scattering is facilitated by linking CRP to latex particles
- hsCRP (sample) + anti-hsCRP antibody → complex
- Two measurements spaced 2 weeks are recommended> average them and use the value for monitoring atherosclerotic inflammation
- If CRP is >10 mg/L> invalid and is due to infection or other inflammatory processes

Markers of Pulmonary Embolism

- Embolus lodged in pulmonary arteries, impairing blood flow
- Diagnosis can be challenging due to similarities with other conditions, such as ACS
- Often, no signs or symptoms present
- Classical presentation of PE: dyspnea, tachycardia, tachypnea, coughing
- Deep vein thrombosis (DVT)

Markers of Pulmonary Embolism (cont'd)



CASE STUDY 26-3

An 83-year-old man with known severe coronary artery disease, diffuse small vessel disease, and significant stenosis distal to a vein graft from previous CABG surgery was admitted when his physician referred him to the hospital after a routine office visit. His symptoms included 3+ pedal edema, jugular vein distention, and heart sound abnormalities. Significant laboratory data obtained on admission were as follows:

Urea nitrogen (6–24 mg/dL)	53
Creatinine (0.5–1.4 mg/dL)	2.2
Total protein (6.0–8.3 g/dL)	5.8
Albumin (3.5–5.3 g/dL)	3.2
Glucose (60–110 mg/dL)	312
Calcium (4.3–5.3 mmol/L)	4.1
Phosphorus (2.5–4.5 mg/dL)	2.4
Total CK (54–186 U/L)	134
CK-MB (0–5 ng/L)	4
% CK-MB (<6%)	3
Myoglobin (<70 µg/L)	62
Troponin T (0–0.1 µg/L)	0.2

Questions

1. Do the symptoms of this patient suggest acute MI?
2. Based on the preceding laboratory data, would this diagnosis be acute MI? Why or why not?
3. Based on the preceding laboratory data, are there other organ system abnormalities present?
4. What are the indicators of these organ system abnormalities?
5. Is there a specific laboratory test that might indicate congestive heart failure in this patient?

CASE STUDY 26-4

A 68-year-old man presented to the emergency department with sudden onset of chest pain, left arm pain, dyspnea, and weakness while away from home on a business trip. His prior medical history is not available, but he admits to being a 2-pack per day smoker for longer than 20 years.

Cardiac markers were performed at admission and 8 hours postadmission with the following results:

CARDIAC MARKERS	7:30 AM; SEPTEMBER 26	4:00 PM; SEPTEMBER 26
CK-MB (0–5 ng/L)	5.3	9.2
Myoglobin	76	124 (<70 µg/L)
Troponin T	<0.1	1.3 (0–0.1 µg/L)

Questions

1. Do these results indicate a specific diagnosis?
2. If so, what is the diagnosis?
3. What myoglobin, CK-MB, and TnT results would be expected if assayed at 4 PM on September 27?
4. Can any assumptions be made about the patient's lifestyle/habits/health that would increase his risk for this condition?
5. Are there any assays that might indicate his risk for further events of this type?

CASE STUDY 26-5

A 48-year-old woman was seen by her primary physician for a routine physical examination. Her father and his brother died before the age of 55 with acute MI and another uncle had CABG surgery at age 52. Because of this family history, she requested for any testing that might indicate a predisposition or increased risk factors for early cardiac disease. She does not smoke, does not have hypertension, is approximately 20 lb overweight, and exercises moderately. The following test results were obtained.

Total cholesterol (<200 mg/dL)	187 mg/dL
HDL cholesterol (30–75 mg/dL)	52 mg/dL
LDL cholesterol (60–130 mg/dL)	95 mg/dL
Lipoprotein(a) (<30 mg/dL)	34 mg/dL
Triglycerides (60–160 mg/dL)	203 mg/dL
Glucose (60–110 mg/dL)	83 mg/dL
Total CK (15–130 IU/L)	65 IU/L
CK-MB (<8 IU/L)	1.9 IU/L
% CK-MB (0–6%)	3
Homocysteine (<15 µmol/L)	18 µmol/L
Fibrinogen (2–4.5 mg/dL)	4.3 mg/dL
D-dimer (0–250 µg/mL)	160 µg/mL
hsCRP (0.016–0.76 mg/dL)	0.91 mg/dL

Questions

1. Do any of the results obtained indicate a high risk for development of cardiac disease? If so, which results?
2. Does this patient have risk factors for early cardiac disease that can be modified by diet or lifestyle modifications? If so, what changes can be made?
3. Is there any specific treatment that can be instituted to reduce this patient's risk?
4. How should this patient be monitored?