Pathophysiology

Cardiovascular disorder

Coronary heart disease

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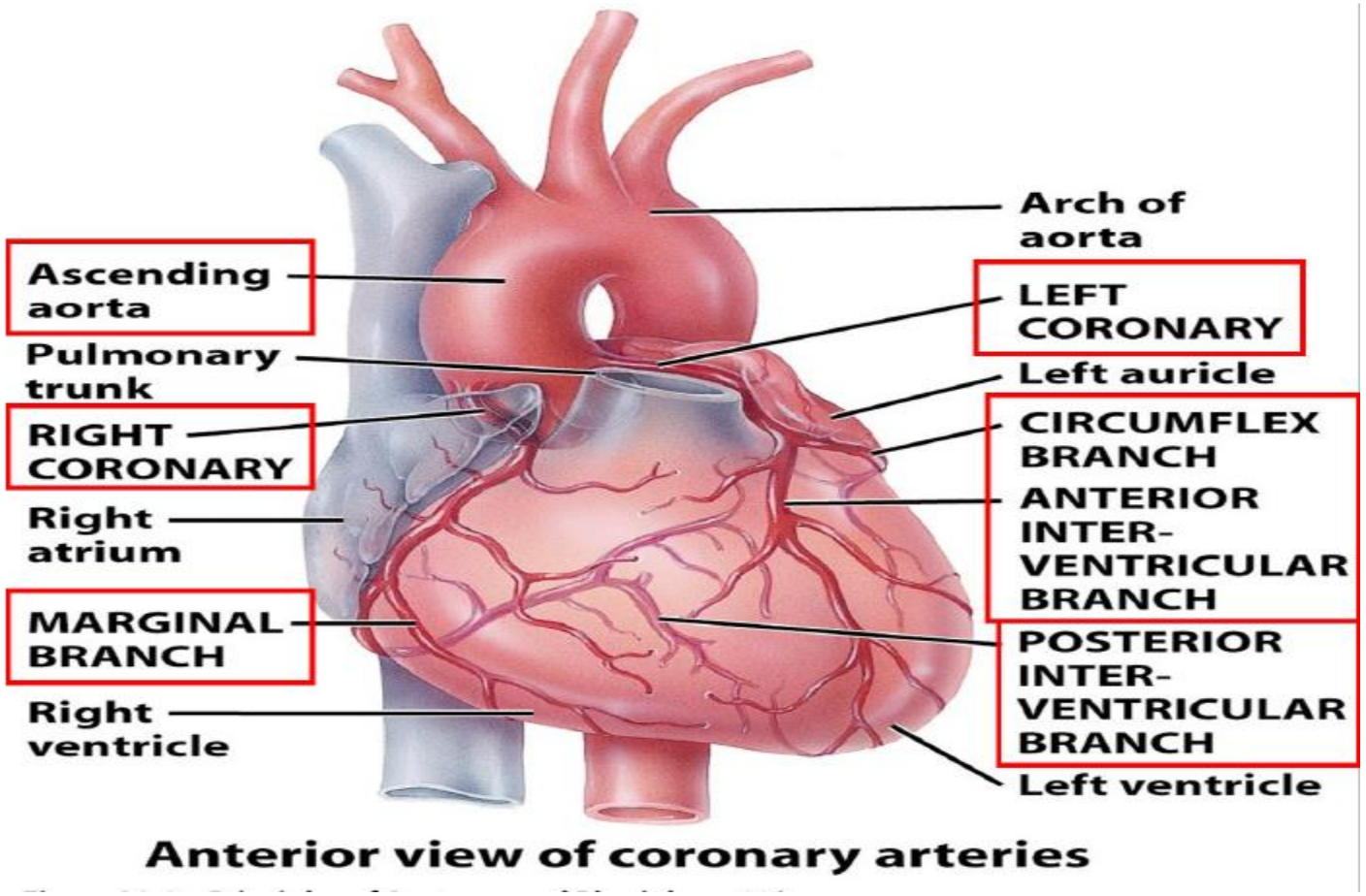


Anterior view of coronary arteries

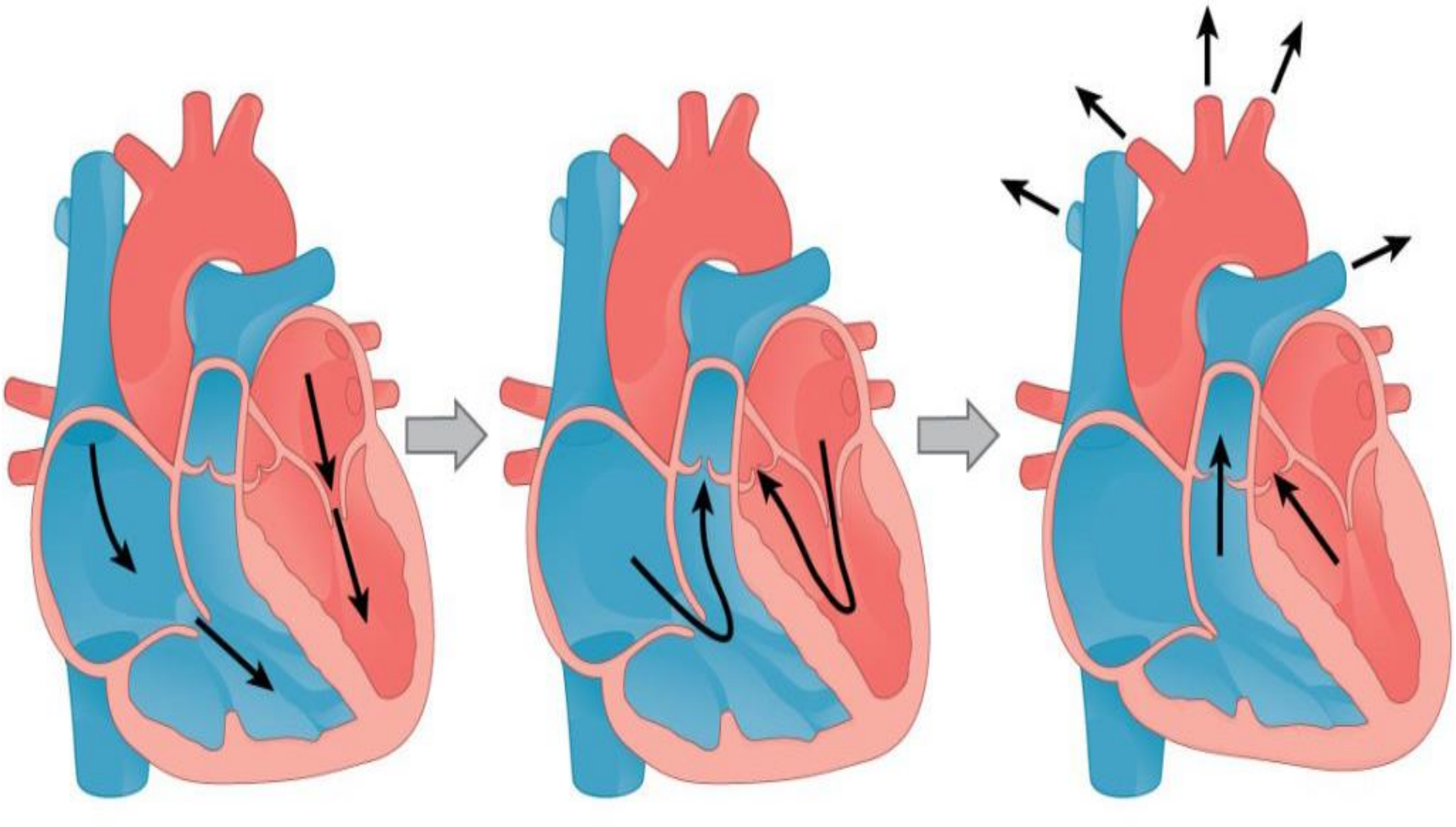
The heart is a pump that supplies all tissues and organs of the body with oxygen-rich blood. The heartbeat is caused by the heart muscles relaxing and contracting. During this cycle, the period of relaxation is called diastole and the period of contraction is called systole. Diastole is defined by the following characteristics:

Diastole is when the heart muscle relaxes.

When the heart relaxes, the chambers of the heart fill with blood, and a person's blood pressure decreases

Systole is defined by the following characteristics:

Systole is when the heart muscle contracts. When the heart contracts, it pushes the blood out of the heart and into the large blood vessels of the circulatory system. From here, the blood goes to all of the organs and tissues of the body. During systole, a person's blood pressure increase



(a) **Cardiac diastole**: all chambers are relaxed, and blood flows into the heart.

(b) **Atrial systole, ventricular diastole**: atria contract, pushing blood into the ventricles.

(c) **Atrial diastole, ventricular systole**: after the atria relax, the ventricles contract, pushing blood out of the heart.

Coronary Artery Disease:

- The term coronary artery disease refers to disorders of myocardial blood flow due to stable or unstable coronary atherosclerotic plaques.
- Unstable atherosclerotic plaques tend to fissure or rupture, causing platelet aggregation and potential for thrombus formation with production of a spectrum of acute coronary syndromes of increasing severity, ranging from unstable angina, to non–ST-segment elevation myocardial infarction, to ST-segment elevation myocardial infarction.
- Stable atherosclerotic plaques produce fixed obstruction of coronary blood flow with myocardial ischemia occurring during periods of increased metabolic need, such as in stable angina.

Coronary artery disease (CAD) :(CORONARY HEART DISAESE)

The term coronary artery disease (CAD) describes heart disease caused by impaired coronary blood flow. In most cases, CAD is caused by atherosclerosis, which affects not only the coronary arteries but arteries in other areas of the body. Diseases of the coronary arteries can cause myocardial ischemia and angina, myocardial infarction or heart attack, cardiac arrhythmias, conduction defects, heart failure, and sudden death. Each year, more than 1.6 million Americans have new or recurrent myocardial infarctions; one third of those die within the first 24 hours, and many of those who survive suffer significant morbidity.

Major risk factors for CAD include :

- cigarette smoking
- elevated blood pressure
- elevated serum total and low-density lipoprotein (LDL) cholesterol,
- low serum high-density lipoprotein (HDL) cholesterol
- diabetes
- advancing age
- metabolic syndrome

Myocardial Oxygen Supply and Demand:

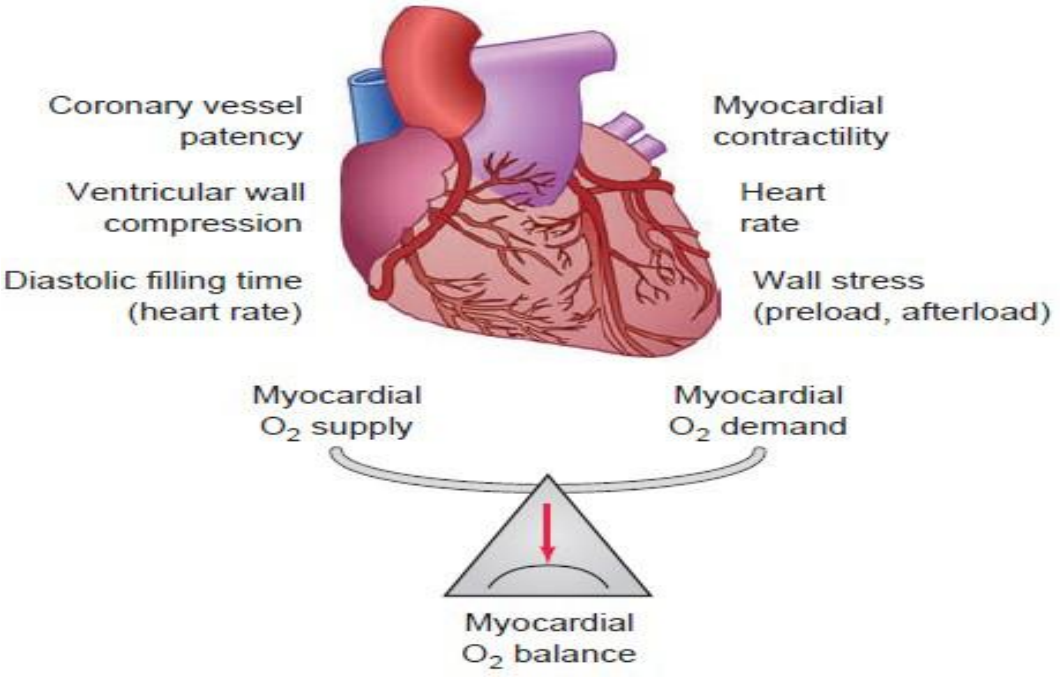
The coronary circulation supplies the heart muscle with the oxygen and nutrients it needs to pump blood out to the rest of the body. In a person who is resting, 75% of the oxygen in the blood that passes through the myocardium is extracted. As the metabolic needs of the body change, cardiac function and coronary blood flow must adapt to meet these needs. If there is an imbalance in the myocardial oxygen supply and demand, myocardial ischemia and angina, myocardial infarction, or even sudden death can occur.

Myocardial Oxygen Supply: Myocardial oxygen supply is determined by the coronary arteries and capillary inflow and the ability of hemoglobin to transport and deliver oxygen to the heart muscle. Important factors in the transport and delivery of oxygen include the fraction of inspired oxygen in the blood and the number of red blood cells with normally functioning hemoglobin. Even with adequate coronary blood flow, myocardial ischemia can occur in situations of hypoxia, anemia, or carbon monoxide poisoning.

Myocardial Oxygen Demand: There are three major determinants of myocardial oxygen demand (MVO2): the heart rate, left ventricular contractility, and systolic pressure or myocardial wall stress or tension. The heart rate is the most important factor in myocardial oxygen demand, for two reasons:

1. As the heart rate increases, myocardial oxygen consumption or demand also increases.

2. Subendocardial coronary blood flow is reduced because of the decreased diastolic filling time with increased heart rates.



Assessment of Coronary Blood Flow and Myocardial Perfusion:

Among the methods used in the evaluation of coronary blood flow and myocardial perfusion are electrocardiography, exercise stress testing, echocardiography, and Doppler ultrasonographic imaging; cardiac MRI and CT; and cardiac catheterization and angiography. These assessment modalities vary widely and are undergoing constant technological advances.

Electrocardiography. The 12-lead ECG is the most frequently used cardiovascular diagnostic procedure.

Exercise Stress Testing. Exercise stress testing is a means of observing cardiac function under stress and is typically performed in adults with symptoms of known or suspected ischemic heart disease.

Echocardiography. Echocardiography is still the most widely used diagnostic test to check for structure and function of the heart.

Nuclear Cardiac Imaging. Nuclear cardiac imaging techniques involve the use of radionuclides

(i.e., radioactive substances) and are essentially noninvasive.

Cardiac Magnetic Resonance Imaging(MRI) and Computed Tomography(CT). The cardiac MRI creates a spatially resolved map of radio signals and, compared with x-ray–based techniques, is much safer

Cardiac Catheterization and Arteriography. Cardiac catheterization is one of the most widely used invasive procedures in the assessment of CAD.

Coronary Atherosclerosis and the Pathogenesis of Coronary Artery Disease

Atherosclerosis is the most common cause of CAD, is slow and progressive, and can begin at a very young age in the United States and other developed countries of the world.

Atherosclerosis can affect one or all three of the major epicardial coronary arteries and their branches. Clinically significant lesions may be located anywhere in these vessels, but tend to predominate in the first several centimeters of the left anterior descending and left circumflex or the entire length of the right coronary artery. Sometimes the major secondary branches also are involved.

Coronary artery disease is commonly divided into two types of disorders:

the acute coronary syndrome and chronic ischemic heart disease. The acute coronary syndrome (ACS) represents a spectrum of acute ischemic heart diseases ranging from unstable angina to myocardial infarction resulting from disruption of an atherosclerotic plaque.

Chronic ischemic heart disease is characterized by recurrent and transient episodes of myocardial ischemia and stable angina that result from narrowing of a coronary artery lumen due to atherosclerosis and/or vasospasm.

Stable versus Unstable Plaque.

There are two types of atherosclerotic lesions:

- Fixed or stable plaque, which obstructs blood flow
- Unstable/vulnerable plaque or high-risk plaque, which can rupture and cause platelet adhesion and thrombus formation

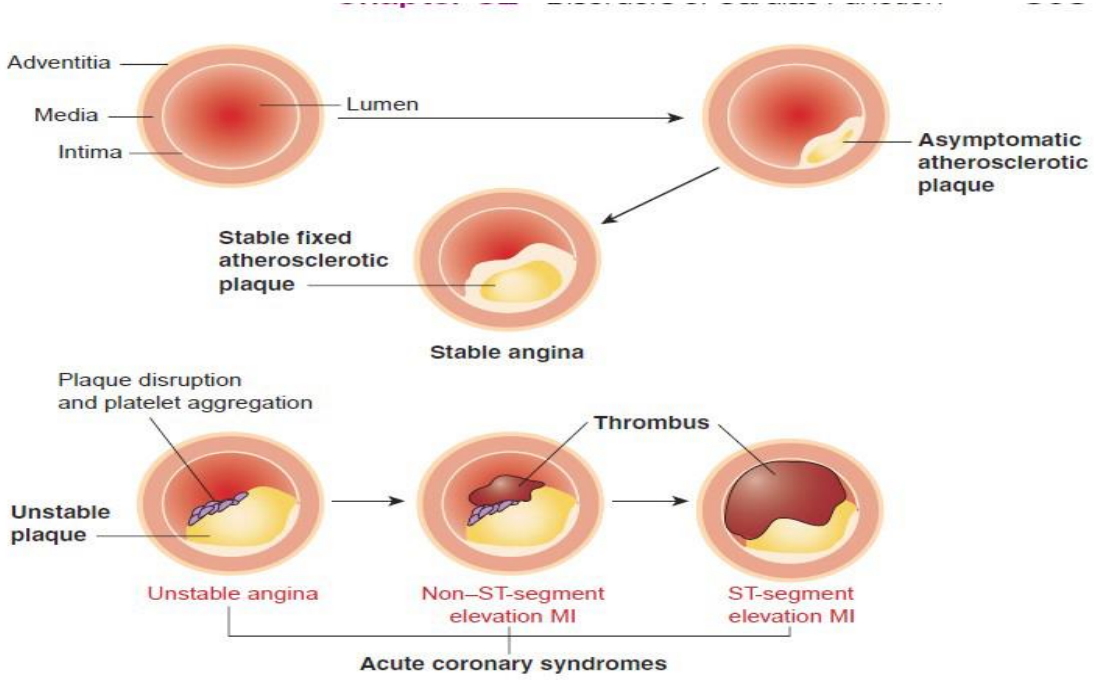


FIGURE 32.5 • Atherosclerotic plaque: stable fixed atherosclerotic plaque in stable angina and unstable plaque with plaque disruption and platelet aggregation in the acute coronary syndromes.

The major determinants of plaque vulnerability to disruption include the size of the lipid-rich core, the stability and thickness of its fibrous cap, the presence of inflammation, and the lack of smooth muscle cells (Fig. 32.5). Plaques with a thin fibrous cap overlaying a large lipid core are at high risk for rupture. Although plaque disruption may occur spontaneously, it is often triggered by hemodynamic factors such as blood flow characteristics and vessel tension. For example, a sudden surge of sympathetic activity with an increase in blood pressure, heart rate, force of cardiac contraction, and coronary blood flow is thought to increase the risk of plaque disruption. Indeed, many people with myocardial infarction report a trigger event, most often emotional stress or physical activity.

Plaque disruption also has a diurnal variation, occurring most frequently during the first hour after arising, suggesting that physiologic factors such as surges in coronary artery tone and blood pressure may promote atherosclerotic plaque disruption and subsequent platelet deposition. It has been suggested that the sympathetic nervous system is activated on arising, resulting in changes in platelet aggregation and fibrinolytic activity that tend to favor thrombosis.

Thrombosis and Vessel Occlusion

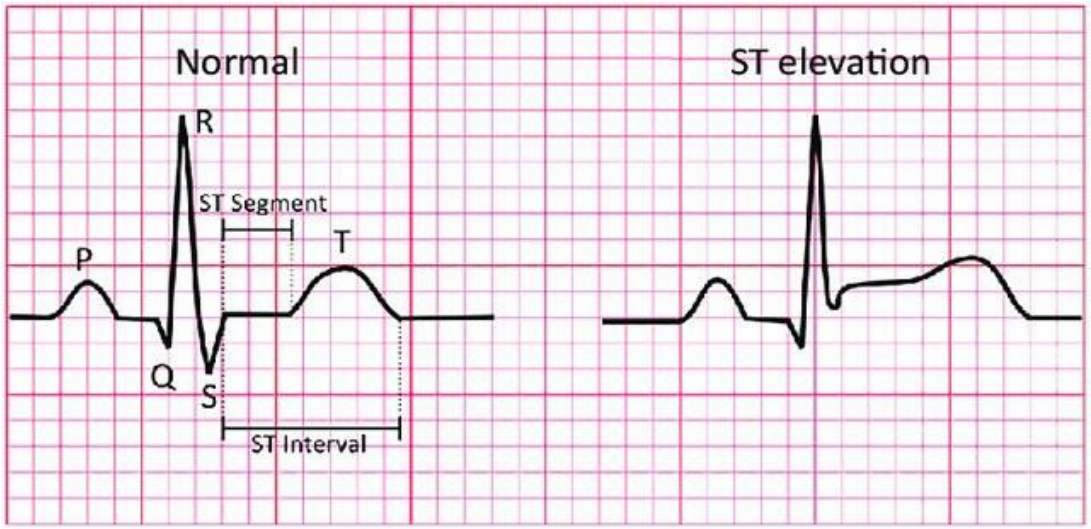
Local thrombosis occurring after plaque disruption results from a complex interaction among its lipid core, smooth muscle cells, macrophages, and collagen. The lipid core provides a stimulus for platelet aggregation and thrombus formation. Both smooth muscle and foam cells in the lipid core contribute to the expression of tissue factor in unstable plaques. Once exposed to blood tissue factor initiates the extrinsic coagulation pathway, resulting in the local generation of thrombin and deposition of fibrin.

Platelets play an important role in linking plaque disruption to acute CAD. As a part of the response to plaque disruption platelets adhere to the endothelium and release substances (i.e.,adenosine diphosphate [ADP], thromboxane A2, and thrombin) that promote further aggregation of platelets and thrombus formation. The platelet membrane, which contains glycoprotein receptors that bind fibrinogen and link platelets together, contributes to thrombus formation.

Platelet adhesion and aggregation occurs in several steps. First, release of ADP, thromboxane A2, and thrombin initiates the aggregation process. Second, glycoprotein IIb/IIIa receptors on the platelet surface are activated. Third, fibrinogen binds to the activated glycoprotein receptors, forming bridges between adjacent platelets.

Acute Coronary Syndrome:

- Acute coronary syndrome includes unstable angina, non– ST-segment elevation (non–Q-wave) myocardial infarction, and ST-segment elevation (Q-wave) myocardial infarction.
- Persons without ST-segment elevation on ECG are those in whom thrombotic coronary occlusion is subtotal or intermittent, whereas those with ST-segment elevation are usually found to have complete coronary occlusion on angiography, and many ultimately have Q-wave myocardial infarction.



- **Electrocardiographic Changes**
- The classic ECG changes that occur with ACS involve T-wave inversion, ST-segment elevation, and development of an abnormal Q wave. The changes that occur may not be present immediately after the onset of symptoms and vary Considerably depending on the duration of the ischemic event (acute versus evolving), its extent (subendocardial versus transmural), and its location (anterior versus inferior posterior).
- **Serum biomarkers for ACS include** cardiac-specific troponin I (TnI) and troponin T (TnT) and creatine kinase MB (CK-MB). As the myocardial cells become necrotic, their intracellular contents begin to diffuse into the surrounding interstitium and then into the blood.
- The troponin assays have high specificity for myocardial tissue and have become the primary biomarker tests for the diagnosis of myocardial infarction.
- The troponin complex, which is part of the actin filament, consists of three subunits(i.e., troponin C [TnC], TnT, and TnI) that regulate calcium mediated actin–myosin contractile process in striated muscle. TnI and TnT, which are present in cardiac muscle, begin to rise within 3 hours after the onset of myocardial infarction and may remain elevated for 7 to 10 days after the event. This is especially advantageous in the late diagnosis of myocardial infarction

- **Creatine kinase is an intracellular** enzyme found in muscle cells. There are three isoenzymes of CK, with the MB isoenzyme being highly specific for injury to myocardial tissue. Serum levels of CK-MB exceed normal ranges within 4 to 8 hours of myocardial injury and decline to normal within 2 to 3 days. When comparing troponin and CK-MB, the troponin level identifies necrosis in cardiac muscles earlier then CK-MB. Clinicians examining cardiac biomarkers should focus on troponin levels, rather than CK-MB levels, for diagnosis and establishing the success of reperfusion.
- **Unstable Angina/Non–ST-Segment Elevation Myocardial Infarction:**
- Persons who have no evidence of serum markers for myocardial damage are considered to have UA, whereas a diagnosis of NSTEMI is indicated if a serum marker of myocardial injury is present.
- The pathophysiology of UA/NSTEMI can be divided into five phases:

1. The development of the unstable plaque that ruptures or plaque erosion with superimposed nonocclusive thrombosis
2. An obstruction such as spasm, constriction, dysfunction, or adrenergic stimuli
3. Severe narrowing of the coronary lumen
4. Inflammation
5. Any physiological state causing ischemia related to decreased oxygen supply such as fever or hypotension

- Inflammation can play a prominent role in plaque instability, with inflammatory cells releasing cytokines that cause the fibrous cap to become thinner and more vulnerable to rupture or erosion.
- The pain associated with UA/NSTEMI has a persistent and severe course and is characterized by at least one of three features:

1. It occurs at rest (or with minimal exertion), usually lasting more than 20 minutes (if not interrupted by nitroglycerin).

2. It is severe and described as frank pain and of new onset (i.e., within 1 month).

3. It is more severe, prolonged, or frequent than previously experienced.

UA/NSTEMI is classified by severity based on clinical history, ECG pattern, and serum biomarkers.

- UA/NSTEMI is classified as:
- Class I (new onset severe angina)
- Class II (angina at rest within the past month, but not within the last 48 hours)
- Class III (angina at rest within 48 hours)
- The ECG pattern in UA/NSTEMI demonstrates ST-segment depression (or transient ST-segment elevation) and T-wave changes. The degree of ST-segment deviation has been shown to be an important measure of ischemia and prognosis

- **ST-Segment Elevation Myocardial Infarction:**
- Acute STEMI, also known as heart attack, is characterized by the ischemic death of myocardial tissue associated with atherosclerotic disease of the coronary arteries. The area of infarction is determined by the coronary artery that is affected and by its distribution of blood flow.
- Pathophysiology.
- The extent of the infarct depends on the location and extent of occlusion, amount of heart tissue supplied by the vessel, duration of the occlusion, metabolic needs of the affected tissue, extent of collateral circulation, and other factors such as heart rate, blood pressure, and cardiac rhythm.
- An infarct may involve the endocardium, myocardium, epicardium, or a combination of these. The principal biochemical consequence of myocardial infarction is the conversion from aerobic to anaerobic metabolism with inadequate production of energy to sustain normal myocardial function. As a result, a striking loss of contractile function occurs within 60 seconds of onset. Changes in cell structure (i.e., glycogen depletion and mitochondrial swelling) develop within several minutes. These early changes are reversible if blood flow is restored.

- Although gross tissue changes are not apparent for hours after onset of myocardial infarction, the ischemic area ceases to function within a matter of minutes, and irreversible damage to cells occurs in approximately 40 minutes. Irreversible myocardial cell death (necrosis) occurs after 20 to 40 minutes of severe ischemia.
- Microvascular injury occurs in approximately 1 hour and follows irreversible cell injury. If the infarct is large enough, it depresses overall left ventricular function and pump failure ensues. Multiple dynamic structural changes maintain cardiac function in persons with STEMI. Both the infarcted and non infarcted areas of the ventricle undergo progressive changes in size, shape, and thickness, comprising early wall thinning, healing, hypertrophy, and dilation, collectively termed ventricular remodeling.
- **Clinical Manifestations:**
- STEMI may occur as an abrupt onset event or as a progression from UA/NSTEMI. The onset of STEMI usually is abrupt, with pain as the significant symptom.
- The pain typically is severe and crushing, often described as being constricting, suffocating, or like “something sitting on my chest.” It usually is substernal, radiating to the left arm, neck, or jaw, although it may be experienced in other areas of the chest.

- Unlike that of angina, the pain associated with STEMI is more prolonged and not relieved by rest or nitroglycerin, and narcotics frequently are required. Some persons may not describe it as “pain,” but as “discomfort.” Women often experience atypical ischemic-type chest discomfort,
- whereas the elderly may complain of shortness of breath more frequently than chest pain.
- **Gastrointestinal complaints**
- are common with STEMI. There may be a sensation of epigastric distress; nausea and vomiting may occur. These symptoms are thought to be related to the severity of the pain and vagal stimulation. The epigastric distress may be mistaken for indigestion, and the person may seek relief with antacids or other home remedies, which only delays getting medical attention. Complaints of fatigue and weakness, especially of the arms and legs, are common. Pain and sympathetic stimulation combine to give rise to tachycardia, anxiety, restlessness, and feelings of impending doom.
- A productive cough may be present with frothy, pink sputum. The skin often is pale, cool, and moist. Impairment of myocardial function may lead to hypotension and shock.
- Sudden death from STEMI is death that occurs within 1 hour of symptom onset. It usually is attributed to fatal arrhythmias, which may occur without evidence of infarction.
- Early hospitalization after onset of symptoms greatly improves the chances of averting sudden death because appropriate resuscitation facilities are immediately available when the ventricular arrhythmia occurs.

Management of Acute Coronary Syndrome

- Because the specific diagnosis of STEMI often is difficult to make at the time of entry into the health care system, the immediate management of UA/NSTEMI and STEMI is generally the same. The prognosis in STEMI is largely related to the occurrences of two general complications arrhythmias and mechanical complications (pump failure). The majority of deaths from STEMI are due to the sudden development of ventricular arrhythmias.
- **Commonly indicated treatment regimens include :**
- Administration of oxygen, aspirin, nitrates, pain medications, antiplatelet and anticoagulant therapy, and β-adrenergic blocking agents (beta-blockers).
- People with ECG evidence of infarction should receive immediat reperfusion therapy with a thrombolytic agent or PCI within 60 to 90 minutes.
- The importance of intensive insulin control to maintain normal blood glucose (80 to 110 mg/dL) in people who are critically ill has been supported by multiple studies.