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OF EXCELLENCE

10th
Edition

TEXTBOOK OF PATHOLOGY

As per the Revised Competency-based
Medical Education Curriculum (NMC)

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Detailed Contents

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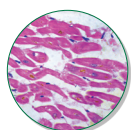
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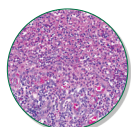
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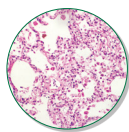
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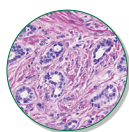
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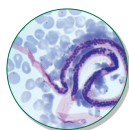
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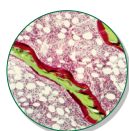
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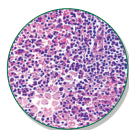
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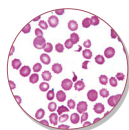
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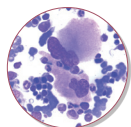
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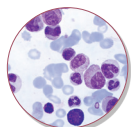
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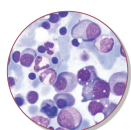
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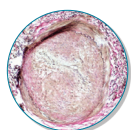
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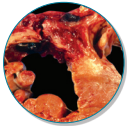
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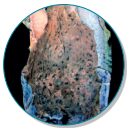
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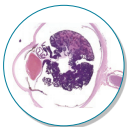
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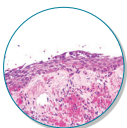
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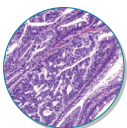
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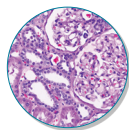
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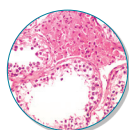
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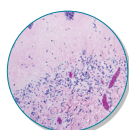
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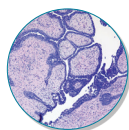
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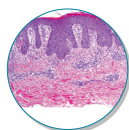
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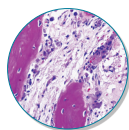
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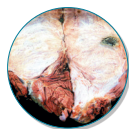
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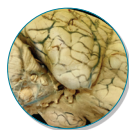
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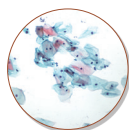


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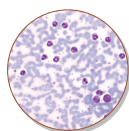
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Chapter 17

The Heart

CHAPTER OUTLINE

The heart is the most important organ in the body for preserving life. It is a muscular pump that ejects blood into the vascular tree with sufficient pressure to maintain optimal circulation to various organs and tissues. Thus, the heart and blood vessels together function as a cardiovascular unit to meet the perfusion requirements of the body. Currently, cardiovascular diseases (CVDs) are the most prevalent disorders, accounting for the maximum number of deaths globally, more so due to industrialization, urbanization, and associated lifestyle changes. Predominant forms of CVDs include rheumatic valvular disease, hypertension, coronary heart disease, and stroke.

From the point of view of the pathological study of heart diseases, they are best understood in the context of its normal structure and function, and then learn about diseases relating to the three anatomic elements that comprise the heart, namely the endocardium, the myocardium, and the pericardium. However, it is generally not always possible to describe heart diseases confined to a single anatomic boundary of the heart, as many heart diseases may involve other layers of the heart as well.

In view of this, heart diseases are described in this chapter under the following headings based on the rational combination of the anatomic region involved and the functional impairment produced: 1) normal structure and function, 2) heart failure, 3) congenital heart diseases, 4) ischemic heart disease, 5) rheumatic fever and rheumatic heart disease, 6) non-rheumatic endocarditis, 7) valvular diseases and deformities, 8) other myocardial diseases, 9) pericardial disease, 10) tumors of the heart, and 11) pathology of cardiovascular interventions.

NORMAL STRUCTURE

ANATOMY AND PHYSIOLOGY

The average weight of the heart in an adult male is 300–350 g, while in an adult female it is 250–300 g. The heart is divided into four chambers: a right and a left atrium, both located superiorly, and a right and a left ventricle, both located inferiorly. The atria are separated by a thin interatrial partition called the *interatrial septum*, while the ventricles are separated by a thick muscular partition called the *interventricular septum*. The thickness of the right ventricular wall is 0.3–0.5 cm, while that of the left ventricular wall is 1.3–1.5 cm. The blood flow through the heart chambers follows a specific pathway (**Fig. 17.1**): venous blood from systemic circulation → right atrium → right ventricle → pulmonary arteries → lungs → pulmonary veins → left atrium → left ventricle → aorta → systemic arterial supply.

Transport of blood from the heart is regulated by cardiac valves: two loose flap-like *atrioventricular valves*, the tricuspid on the right and the mitral (bicuspid) on the left; and two *semilunar valves* with three leaflets each, the pulmonary and aortic valves, guarding the outflow tracts. The average normal circumference of the valvular openings is approximately 12 cm

for the tricuspid, 8.5 cm for the pulmonary, 10 cm for the mitral, and 7.5 cm for the aortic valve.

The wall of the heart consists mainly of the *myocardium*, which is covered externally by a thin membrane called the *epicardium* or *visceral pericardium*, and lined internally by another thin layer called the *endocardium* (**Fig. 17.2**):

- The **myocardium** is the muscle tissue of the heart, composed of a syncytium of branching and anastomosing, transversely striated muscle fibers or cardiomyocytes arranged in a parallel fashion. The space between myocardial fibers contains a rich capillary network and loose connective tissue. Myocardial fibers are connected to each other by irregular joints known as intercalated discs. These discs represent apposed cell membranes of individual cells, acting as tight junctions for the free transport of ions and action potentials. *Cardiomyocytes* are rich in mitochondria, which are the source of the large amounts of ATP required for cardiac contraction. The cardiac muscle fibers contain an abundant sarcoplasmic reticulum, which corresponds to the endoplasmic reticulum in other cells. Transverse lines divide each fiber into sarcomeres, which serve as structural and functional subunits. Each sarcomere consists of a prominent *central dark A-band*, attributed to thick myosin filaments, flanked on either side by *light I-bands* consisting of

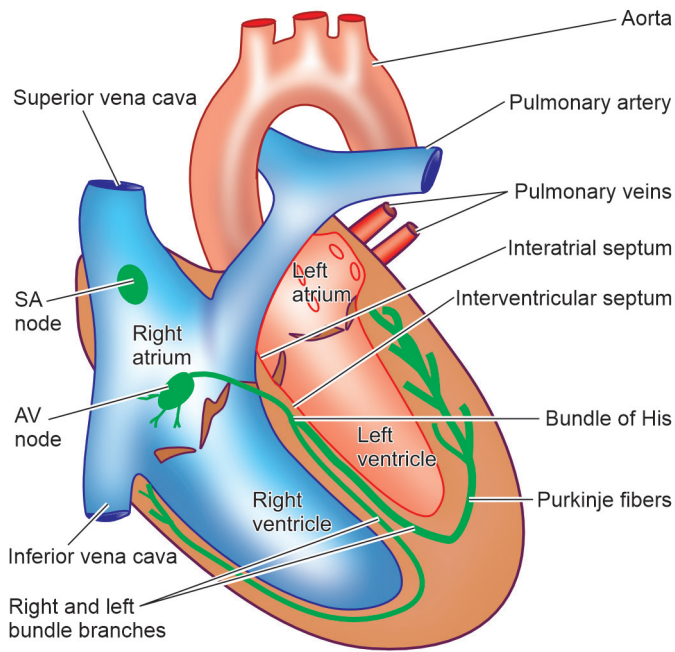


Figure 17.1 The normal anatomic structure of the heart. (SA, sinoatrial; AV, atrioventricular).

thin actin filaments. The actin bands are twisted rods overlying protein molecules called *tropomyosin*. These protein molecules are of three types: troponin-I, troponin-T, and troponin-C. Troponin molecules respond to calcium ions in the cyclical contraction-relaxation of myocardial fibers.

It is important to note that *myocardial fibers are terminally differentiated cells* and do not regenerate. However, recent evidence suggests that new cardiac myocytes can form from stem cells recruited from the circulation.

- The **conduction system of the heart** The conduction system of the heart is located in the myocardium and is responsible for regulating the rate and rhythm of the heart. It is composed of specialized Purkinje fibers, which contain contractile myofilaments and conduct impulses rapidly. The conduction system consists of four major components (**Fig. 17.1**):

1. **Sinoatrial (SA) node** The SA node is in the posterior wall of the right atrium, adjacent to the point at which the superior vena cava enters the heart. It is also known as the cardiac pacemaker as it spontaneously generates electrical impulses, spread across both the atria, causing atrial contraction and blood flowing from atria to corresponding ventricles.

2. **Atrioventricular (AV) node** The AV node is located at the top of the interventricular septum. It receives impulses from the SA node via the AV bundle and transmits them to the bundle of His, after a delay of about 120 milli seconds, to ensure full contraction of atrium and ejection of blood into ventricles.

3. **Atrioventricular (AV) bundle (Bundle of His)** The AV bundle, also known as the bundle of His, conducts impulses from the AV node through the interventricular septum, dividing into right and left bundle branches that arborize in the respective ventricular walls.

4. **Purkinje fibers** These subendocardial fibers transmit impulses from the bundle branches to the ventricular walls, ensuring coordinated contraction of the ventricles.

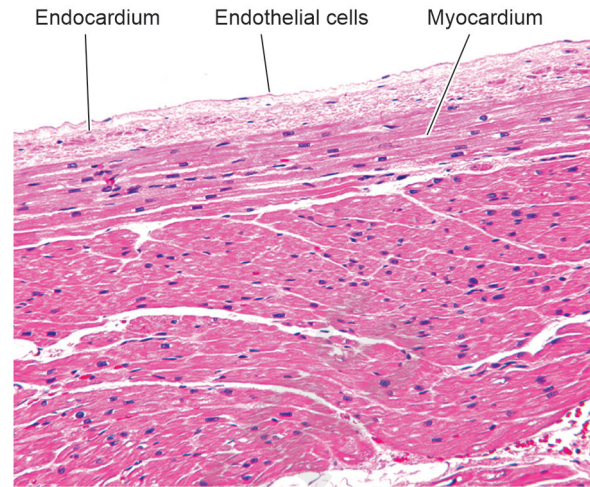


Figure 17.2 Normal microscopic structure of the heart. The endocardium is a thin layer composed of loose connective tissue. The myocardium is composed of striated muscle cells, arranged in syncytium. (Reproduced with permission from *Atlas of Histopathology* by Ivan Damjanov 2012, Jaypee Brothers Medical Publishers Pvt Ltd, New Delhi).

- The **pericardium** consists of two layers—the inner visceral pericardium (or epicardium) and the outer fibrous sac known as the parietal pericardium. These two layers enclose a narrow space called the pericardial cavity, lined by mesothelial cells. It contains 10–30 mL of clear, watery serous pericardial fluid, that acts as a lubricant and shock absorber for the heart.

- The **endocardium** is the smooth, shiny inner lining of the myocardium that covers all the cardiac chambers, valves, chordae tendineae, and papillary muscles. It is lined by endothelium, with connective tissue and elastic fibers in its deeper layers.

- The **heart valves** having the valve cusps and semilunar leaflets, are delicate translucent structures strengthened by collagen and elastic tissue, covered by a layer of endothelium (valvular endocardium).

MYOCARDIAL BLOOD SUPPLY

In order to function optimally, the cardiac muscle requires an adequate supply of oxygen and nutrients. This is facilitated by the coronary arteries, which originate just above the aortic semilunar valve. Interestingly, most of the blood flow to the myocardium occurs during diastole. There are three primary coronary arteries, each supplying blood to specific regions of the heart (**Fig. 17.3**):

1. **Left anterior descending (LAD) coronary artery** supplies blood to most of the apex of the heart, the anterior surface of the left ventricle, a third of the anterior wall of the right ventricle, and the anterior two-thirds of the interventricular septum.

2. **Left circumflex (LCX) coronary artery** supplies the left atrium and a portion of the lateral aspect of the left ventricle.

3. **Right coronary artery (RCA)** supplies the right atrium, the remaining anterior surface of the right ventricle, part of the posterior wall of the left ventricle, and the posterior third of the interventricular septum.

In addition to three main coronaries, another coronary branch of clinical significance is *posterior descending artery (PDA)*, which in majority of cases arises from RCA (85%), or

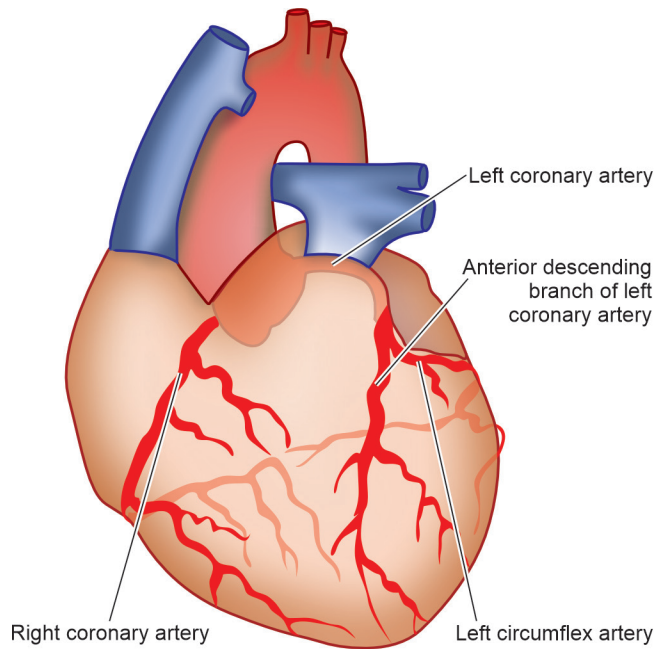


Figure 17.3 Distribution of blood supply to the heart.

from LCX in 10–15% cases, and supplies blood to the posterior third of interventricular septum and the inferior wall.

Coronary veins run parallel to the major coronary arteries, which collect deoxygenated blood after the metabolic needs of myocardial cells are met. This blood is collected into the *coronary sinus*, the largest vein on the posterior surface of the heart, which then drains it into the right atrium.

GLOBAL PATTERNS OF HEART DISEASES

Globally, cardiovascular disease remains the leading cause of premature death in both men and women, accounting for approximately one-fourth of all deaths. The prevalence and types of heart diseases vary significantly in children and adults, and between developing and developed countries due to differences in living standards:

- **In children**, *valvular diseases* are common worldwide. However, in developing countries, infectious causes, particularly rheumatic valvular disease dominates, whereas congenital valvular diseases are more prevalent in developed countries.
- **In adults**, *ischemic heart disease and hypertensive cardiomyopathy* are the predominant cardiac conditions in high-income countries, whereas these conditions are less prevalent in low-income countries.

SUMMARY Normal Structure of Vessels

- **Heart weight** The average weight of the heart is 300–350 g in adult males and 250–300 g in adult females.
- **Ventricular wall thickness** The right ventricular wall is 0.3–0.5 cm thick, while the left ventricular wall is 1.3–1.5 cm thick.
- **Circumference of valvular openings** The average normal circumference of valvular openings is:
 - ◆ Tricuspid valve 12 cm
 - ◆ Pulmonary valve 8.5 cm
 - ◆ Mitral valve 10 cm
 - ◆ Aortic valve 7.5 cm

- **Heart wall structure** The heart wall consists mainly of the myocardium, which is covered externally by the epicardium and lined internally by the endocardium.
- **The conduction system** Located in the myocardium, regulates rate and rhythm of the heart:
 - ◆ Sinoatrial (SA) node is the natural pacemaker of the heart, located in the right atrium.
 - ◆ Atrioventricular (AV) node relays the electrical impulse from the atria to the ventricles.
 - ◆ Bundle of His is the pathway for electrical signals from the AV node to the ventricles.
 - ◆ Purkinje fibers form the network of fibers that distribute electrical impulse throughout the ventricles.
- **Coronary arteries** There are three primary coronary arteries, each supplying blood to specific regions of the heart.
 - ◆ Left anterior descending (LAD) coronary artery Supplies the apex of the heart, the anterior surface of the left ventricle, a third of the anterior wall of the right ventricle, and the anterior two-thirds of the interventricular septum.
 - ◆ Left circumflex (LCX) coronary artery Supplies the left atrium and a portion of the lateral aspect of the left ventricle.
 - ◆ Right coronary artery (RCA) Supplies the right atrium, the remaining anterior surface of the right ventricle, part of the posterior wall of the left ventricle, and the posterior third of the interventricular septum.
- **Coronary sinus** drains deoxygenated blood from the myocardium into the right atrium.

HEART FAILURE

Heart failure is defined as the pathophysiological state in which impaired cardiac function is unable to maintain an adequate circulation for the metabolic needs of the tissues of the body. It may be *acute* or *chronic*. The term congestive heart failure (CHF) is used for the *chronic* form of heart failure in which the patient has evidence of congestion of peripheral circulation and of lungs (page 177). CHF is the end-result of various forms of serious heart diseases.

ETIOLOGY

Heart failure may be caused by one of the following factors, either singly or in combination:

1. INTRINSIC PUMP FAILURE The most common and most important cause of heart failure is weakening of the ventricular muscle due to disease so that the heart fails to act as an efficient pump. The various diseases which may culminate in pump failure by this mechanism are as under:

- Ischemic heart disease
- Myocarditis
- Cardiomyopathies
- Metabolic disorders, e.g. beriberi
- Disorders of the rhythm, e.g. atrial fibrillation and flutter

2. INCREASED WORKLOAD ON THE HEART Increased mechanical load on the heart results in increased myocardial demand resulting in myocardial failure. Increased load on the heart may be in the form of pressure load or volume load.

- Increased pressure load** may occur in the following states:

- a) Systemic and pulmonary arterial hypertension
- b) Valvular disease, e.g. mitral stenosis, aortic stenosis, pulmonary stenosis
- c) Chronic lung diseases
- ii) **Increased volume load** occurs when a ventricle is required to eject more than normal volume of blood resulting in cardiac failure. This is seen in the following conditions:
 - a) Valvular insufficiency
 - b) Severe anemia
 - c) Thyrotoxicosis
 - d) Arteriovenous shunts
 - e) Hypoxia due to lung disease

3. IMPAIRED FILLING OF CARDIAC CHAMBERS Decreased cardiac output and cardiac failure may result from extracardiac causes or defect in filling of the heart:

- i) Cardiac tamponade, e.g. hemopericardium, hydropericardium
- ii) Constrictive pericarditis

TYPES OF HEART FAILURE

Heart failure may be acute or chronic; right-sided or left-sided.

ACUTE AND CHRONIC HEART FAILURES

Depending upon whether heart failure develops rapidly or slowly, it may be acute or chronic.

Acute heart failure Sudden and rapid development of heart failure occurs in the following conditions:

- i) Large myocardial infarction
- ii) Valve rupture
- iii) Cardiac tamponade

- iv) Massive pulmonary embolism
- v) Acute viral myocarditis
- vi) Acute bacterial toxemia

In acute heart failure, there is sudden reduction in cardiac output resulting in systemic hypotension, but edema does not appear. Instead, a state of cardiogenic shock and cerebral hypoxia develops.

Chronic heart failure More often, heart failure develops slowly as observed in the following states:

- i) Myocardial ischemia from atherosclerotic coronary artery disease
- ii) Multivalvular heart disease
- iii) Systemic arterial hypertension
- iv) Chronic lung diseases resulting in hypoxia and pulmonary arterial hypertension
- v) Progression of acute into chronic failure

In chronic heart failure, compensatory mechanisms like tachycardia, cardiac dilatation and cardiac hypertrophy try to maintain cardiac output adequate for body organs. This often results in well-maintained arterial pressure and there is appearance of edema.

LEFT-SIDED AND RIGHT-SIDED HEART FAILURES

Though the heart as an organ eventually fails as a whole, functionally the left and right heart act as independent units. From clinical point of view, therefore, it is helpful to consider failure of the left and right heart separately. The clinical manifestations of heart failure result from accumulation of excess fluid *upstream* to the left or right cardiac chamber whichever is initially affected (**Fig. 17.4**):

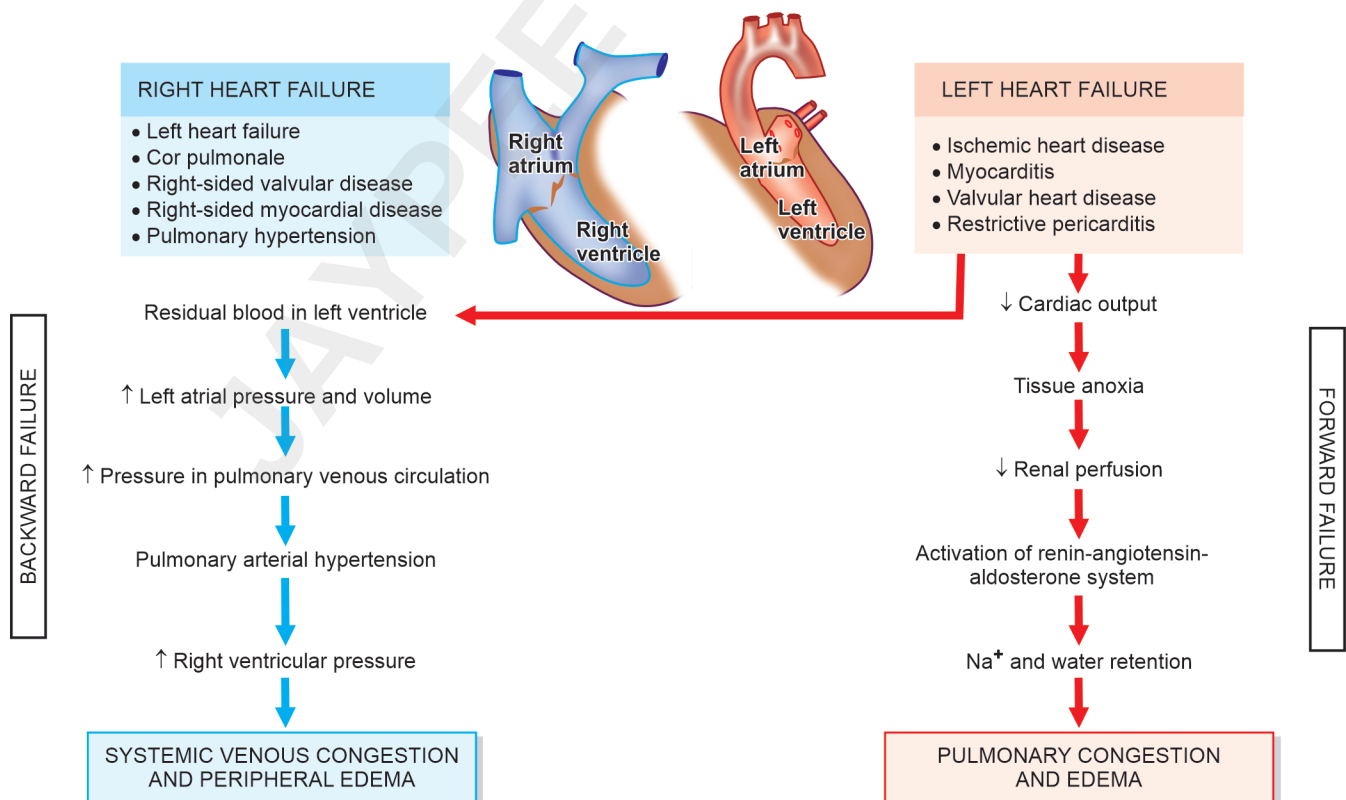


Figure 17.4 Schematic evolution of congestive heart failure and its effects.

Left Heart Failure

It is initiated by stress to the left heart. The major causes are as follows:

- i) Systemic hypertension, most common (discussed below)
- ii) Mitral or aortic valve disease (stenosis)
- iii) Ischemic heart disease
- iv) Myocardial diseases, e.g. cardiomyopathies, myocarditis
- v) Restrictive pericarditis

The clinical manifestations of left-sided heart failure result from decreased left ventricular output, resulting in increased back pressure and accumulation of fluid *upstream* in the lungs. Accordingly, the major pathological changes are as under:

- i) Pulmonary congestion and edema, causing dyspnea and orthopnea (page 177).
- ii) Decreased left ventricular output, causing hypoperfusion and diminished oxygenation of tissues, e.g. in kidneys causing ischemic acute tubular necrosis (page 738), in brain causing hypoxic encephalopathy (page 970), and in skeletal muscles causing muscular weakness and fatigue.

HYPERTENSIVE HEART DISEASE Hypertensive heart disease or hypertensive cardiomyopathy results from systemic hypertension of prolonged duration and manifests as left ventricular hypertrophy. Even mild hypertension (blood pressure higher than 140/90 mm Hg) of sufficient duration may induce hypertensive heart disease. It is the second most common form of heart disease after IHD. As already discussed, hypertension predisposes to atherosclerosis (page 426). Therefore, most patients with hypertensive heart disease have also advanced coronary atherosclerosis and may develop progressive IHD.

Amongst the causes of death in hypertensive patients, cardiac decompensation leading to CHF accounts for about one-third of the cases; other causes of death in patients cases are IHD, cerebrovascular stroke, renal failure following arteriolar nephrosclerosis, dissecting aneurysm of the aorta, and sudden cardiac death.

Pathogenesis Pathogenesis of systemic hypertension is discussed in Chapter 23 (page 748). Here, pathogenesis of left ventricular hypertrophy (LVH), which is most commonly caused by systemic hypertension, is described.

Stimulus to LVH is pressure overload in systemic hypertension. Both genetic and hemodynamic factors contribute to LVH. The stress of pressure on the ventricular wall causes increased production of myofilaments, myofibrils, other cell organelles and nuclear enlargement. Since the adult myocardial fibers do not divide, under increased pressure the fibers are hypertrophied. However, the sarcomeres may divide to increase the cell width.

LVH can be diagnosed by ECG. With aggressive control of hypertension, the left ventricular mass can regress. Abnormalities of diastolic function are more common in hypertension and are present in about one-third of patients with normal systolic function.

Right-sided Heart Failure

Right-sided heart failure occurs more often because of left-sided heart failure. However, some conditions primarily affect

the right ventricle, producing right-sided heart failure. Thus, these causes are as under:

- i) Because of left ventricular failure
- ii) Cor pulmonale or pulmonary heart disease, most common cause (i.e. right heart failure occurring due to intrinsic lung diseases, discussed below)
- iii) Pulmonary or tricuspid valvular disease
- iv) Pulmonary hypertension, secondary to pulmonary thromboembolism
- v) Myocardial disease affecting the right heart
- vi) Congenital heart disease with left-to-right shunt

Whatever the underlying cause, clinical manifestations of right-sided heart failure are *upstream* of the right heart such as systemic (i.e. blood from vena cava) and portal venous congestion and reduced cardiac output. Accordingly, the pathological changes are as under:

- i) Systemic venous congestion in different tissues and organs, e.g. subcutaneous edema on dependent parts, passive congestion of the liver, spleen, and kidneys (page 177), ascites, hydrothorax, congestion of leg veins and neck veins.
- ii) Reduced cardiac output resulting in circulatory stagnation causing anoxia, cyanosis and coldness of extremities.

COR PULMONALE Cor pulmonale (*cor* = heart; *pulmonale* = lung) or pulmonary heart disease is the right heart disease resulting from disorders of the lungs. It is characterized by right ventricular dilatation or hypertrophy, or both. Thus, cor pulmonale is the right-sided counterpart of the hypertensive heart disease that affects the left heart predominantly.

Depending upon the rapidity of development, cor pulmonale may be acute or chronic:

- *Acute cor pulmonale* occurs following massive pulmonary embolism resulting in sudden dilatation of the pulmonary trunk, conus and right ventricle.
- *Chronic cor pulmonale* is more common and is often preceded by chronic pulmonary hypertension (page 504). Following chronic lung diseases can cause chronic pulmonary hypertension and subsequent cor pulmonale:
 - i) Chronic emphysema
 - ii) Chronic bronchitis
 - iii) Pulmonary tuberculosis
 - iv) Pneumoconiosis
 - v) Cystic fibrosis
 - vi) Hyperventilation in marked obesity (Pickwickian syndrome)
 - vii) Multiple organized pulmonary emboli.

Pathogenesis Chronic lung diseases as well as diseases of the pulmonary vessels cause increased pulmonary vascular resistance. The most common underlying mechanisms causing increased pulmonary blood pressure (pulmonary hypertension) is by pulmonary vasoconstriction, activation of coagulation pathway and obliteration of pulmonary arterial vessels. Pulmonary hypertension causes pressure overload on the right ventricle, and hence right ventricular enlargement. Initially, there is right ventricular hypertrophy, but as cardiac decompensation sets in and right heart failure supervenes, dilatation of right ventricle occurs.

The sequence of events involved in the pathogenesis of cor pulmonale is summarized in **Fig. 17.5**.

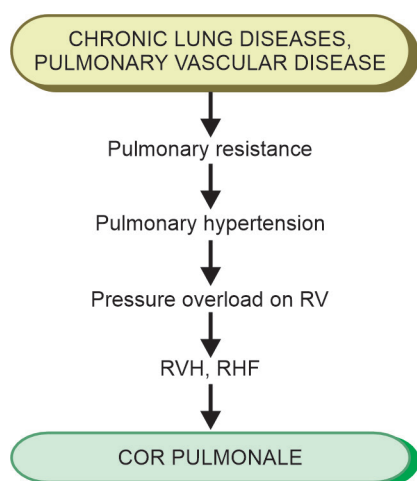


Figure 17.5 Pathogenesis of cor pulmonale. (RV, right ventricle; RVH, right ventricular hypertrophy, RHF, right heart failure).

In summary, in early stage, the *left heart failure* manifests with features of pulmonary congestion and decreased left ventricular output, while the *right heart failure* presents with systemic venous congestion and involvement of the liver and spleen (**Table 17.1**).

COMPENSATORY MECHANISMS: CARDIAC HYPERTROPHY AND DILATATION

To maintain normal cardiac output under either a state of volume overload or contractile defect, several compensatory mechanisms play a role as under:

- Compensatory enlargement in the form of *cardiac hypertrophy, cardiac dilatation, or both*.
- *Tachycardia* (i.e. increased heart rate) due to activation of neurohumoral system, e.g. release of norepinephrine and atrial natriuretic peptide, and activation of renin-angiotensin-aldosterone mechanism.

According to Starling law on pathophysiology of heart, in order to maintain cardiac performance, the failing dilated heart increases the myocardial contractility and thereby attempts to maintain stroke volume. This is achieved by increasing the length of sarcomeres in dilated heart. Ultimately, however, dilatation decreases the force of contraction and leads to residual volume in the cardiac chambers causing volume overload, resulting in cardiac failure that ends in death (**Fig. 17.6**).

CARDIAC HYPERTROPHY

Hypertrophy of the heart is defined as an increase in size and weight of the myocardium. It generally results from increased pressure load, while increased volume load (e.g. valvular incompetence) results in hypertrophy with dilatation of the affected chamber due to regurgitation of the blood through incompetent valve. Atrium may also undergo compensatory changes due to increased workload.

Initially, the hypertrophy of the myocardial fibers is an adaptive response to maintain cardiac function. However, sustained stress leads to pathological hypertrophy by involvement of numerous mediators such as changes in gene transcription, signaling proteins, protein synthesis, calcium handling, metabolism, oxidative stress and inflammation.

CAUSES Hypertrophy with or without dilatation, may involve predominantly the left or the right heart, or both sides.

Left ventricular hypertrophy Common causes are as under:

- Systemic hypertension, most common
- Aortic stenosis and insufficiency
- Mitral insufficiency
- Coarctation of the aorta
- Occlusive coronary artery disease
- Congenital anomalies like septal defects and patent ductus arteriosus
- Conditions with increased cardiac output, e.g. thyrotoxicosis, anemia, arteriovenous fistula

Right ventricular hypertrophy Most of the causes of right ventricular hypertrophy are due to pulmonary arterial hypertension. These are as follows:

- Cor pulmonale from chronic lung diseases (e.g. chronic emphysema, bronchiectasis, pneumoconiosis, pulmonary vascular disease, etc.), most common
- Pulmonary stenosis and insufficiency
- Tricuspid insufficiency
- Mitral stenosis and/or insufficiency
- Left ventricular hypertrophy and failure of the left ventricle

CARDIAC DILATATION

Quite often, hypertrophy of the heart is accompanied by cardiac dilatation. Stress leading to accumulation of excessive volume of blood in a chamber of the heart causes an increase in length of myocardial fibers, and hence cardiac dilatation as a compensatory mechanism.

TABLE 17.1 Comparative features of right heart failure and left heart failure.

	FEATURE	RIGHT HEART FAILURE	LEFT HEART FAILURE
1.	Common causes	i) Secondary to left heart failure ii) Cor pulmonale	i) Systemic hypertension ii) Left ventricular infarct iii) Mitral valve disease
2.	Primary manifestation	Systemic venous congestion	Pulmonary congestion
3.	Common Symptoms	Edema, ascites, hepatomegaly, splenomegaly	Dyspnea, orthopnea, paroxysmal nocturnal dyspnea
4.	Cardiac changes	Right ventricular hypertrophy and dilatation	Left ventricular hypertrophy and decreased output
5.	Pathogenesis	Increased pulmonary vascular resistance → Pressure overload on right ventricle	Pulmonary congestion → Decreased left ventricular output
6.	Organ Involvement	Organs supplied by superior or inferior vena cava	Lungs, and other organs due to inadequate output such as brain

Note: In CHF, however, combined features of both left and right heart failure are noted.

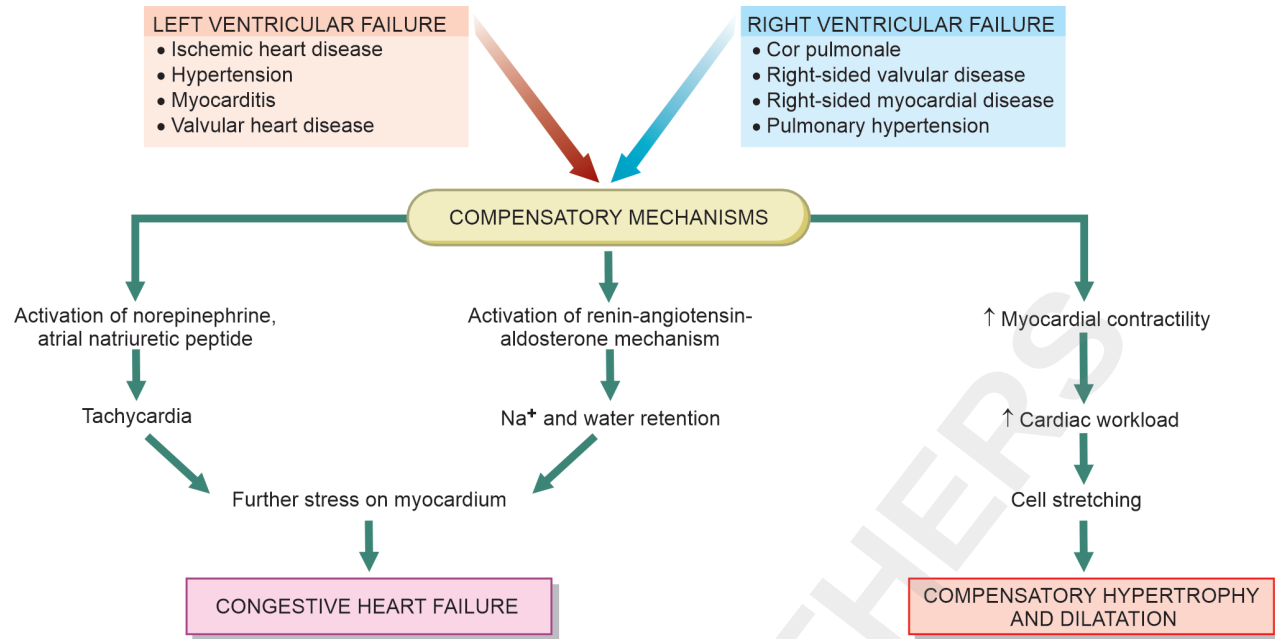


Figure 17.6 Schematic pathophysiology of compensatory mechanisms in cardiac failure.

CAUSES Accumulation of excessive volume of blood within the cardiac chambers from the following causes may result in dilatation of the respective ventricles, or both:

- Valvular insufficiency (mitral and/or aortic insufficiency in left ventricular dilatation, tricuspid and/or pulmonary insufficiency in right ventricular dilatation)
- Left-to-right shunts, e.g. in VSD
- Conditions with high cardiac output, e.g. thyrotoxicosis, arteriovenous shunt
- Myocardial diseases, e.g. cardiomyopathies, myocarditis
- Systemic hypertension

MORPHOLOGY

In heart failure, the heart may show the appearance of concentric or eccentric hypertrophy (**Fig. 17.7**):

- Concentric hypertrophy** of the myocardium is increase in thickness of ventricular wall muscle due to addition of new sarcomeres *in-parallel* to the existing sarcomeres; this occurs in response to high systolic blood pressure.

- Eccentric hypertrophy** of the myocardium, on the other hand, is asymmetrical hypertrophy and dilatation of ventricle that occurs by addition of new sarcomeres *in-series* (i.e. lengthwise) to existing sarcomeres leading to myocardial fiber lengthening; this happens in response to ventricular volume overload.

Grossly, the most significant finding is marked hypertrophy of the heart, chiefly of the left ventricle (**Fig. 17.8**). The weight of the heart increases to 500 g or more (normal weight is about 250–300 g in adults).

- In LVH**, the thickness of the left ventricular wall increases from its normal thickness of 13 to 15 mm up to 20 mm or more. The papillary muscles and trabeculae carneae become rounded and thickened. Initially, there is **concentric hypertrophy** of the left ventricle (without dilatation). But when decompensation and cardiac failure supervene, there is **eccentric hypertrophy** (with dilatation) with thinning of the ventricular wall. In later stage, there may be dilatation and hypertrophy of right heart as well, causing **biventricular hypertrophy**.

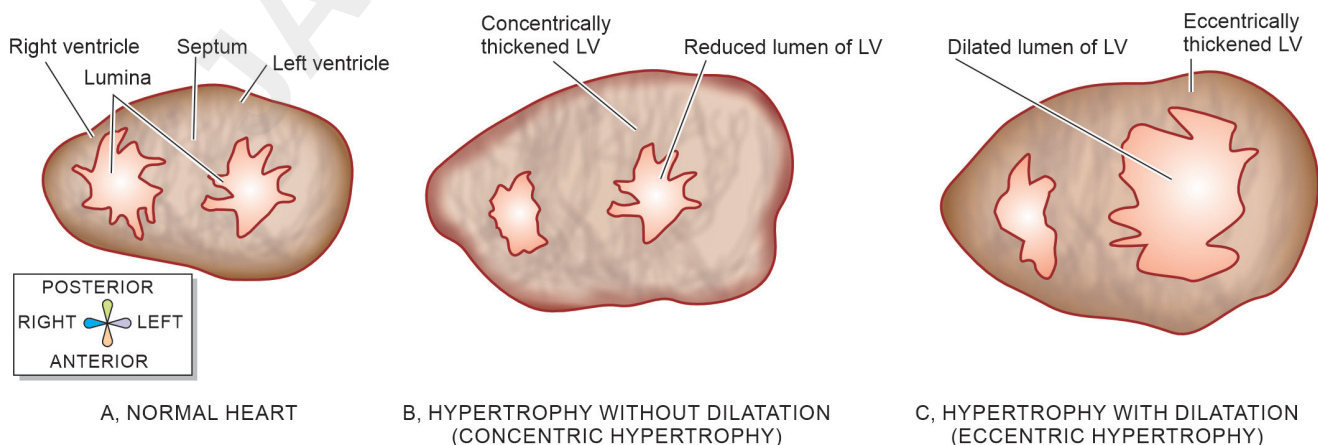


Figure 17.7 Schematic diagram showing transverse section through the ventricles with left ventricular hypertrophy (concentric and eccentric). (LV, left ventricle).

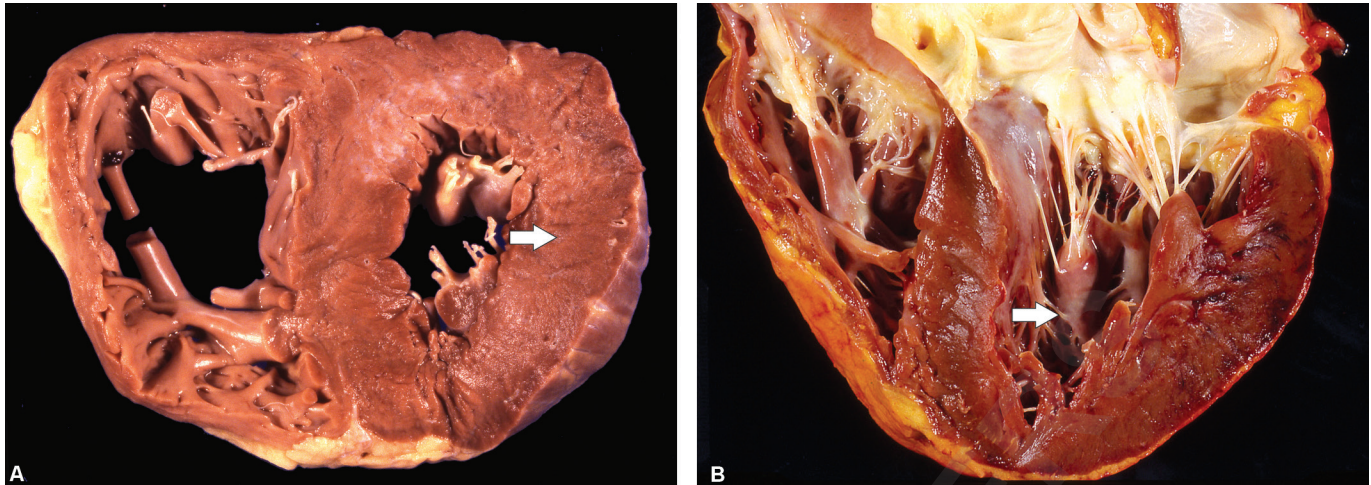


Figure 17.8 A, *Concentric cardiac hypertrophy*. Weight of the heart in this hypertensive deceased is increased. The opened-up chambers show concentric thickening of left ventricular wall (white arrow) with obliterated lumen (hypertrophy without dilatation). B, *Eccentric cardiac hypertrophy*. The heart is heavier. Free walls of both left and right ventricles are thickened (biventricular hypertrophy) while the lumen is dilated (white arrow) (hypertrophy with dilatation). (Images courtesy by Dr Ivan Damjanov, Department of Pathology and Laboratory Medicine, The University of Kansas School of Medicine, Kansas, USA).

- In RVH due to acute cor pulmonale, there is characteristic ovoid dilatation of the right ventricle, and sometimes of the right atrium. In chronic cor pulmonale, there is an increase in thickness of the right ventricular wall from its normal thickness of 3 to 5 mm up to 10 mm or more, causing right ventricular hypertrophy (RVH).

Microscopically, there is an increase in size of individual muscle fibers, fibrosis and disarray of muscle fibers. The myocytes become enlarged, have increased diameter and hyperchromatic nuclei. There may be multiple minute foci of degenerative changes and necrosis in the hypertrophied myocardium (**Fig. 17.9**). These changes appear to arise

because of relative hypoxia of the hypertrophied muscle as the blood supply is inadequate to meet the demands of the increased fiber size. Ventricular hypertrophy renders the inner part of the myocardium more liable to ischemia.

Electron microscopy reveals increase in the number of myofilaments comprising myofibrils, mitochondrial changes and multiple intercalated discs which are active sites for the formation of new sarcomeres. Besides, nucleic acid content determinations have shown an increase in total RNA and increased ratio of RNA to DNA content of the hypertrophied myocardial fibers.

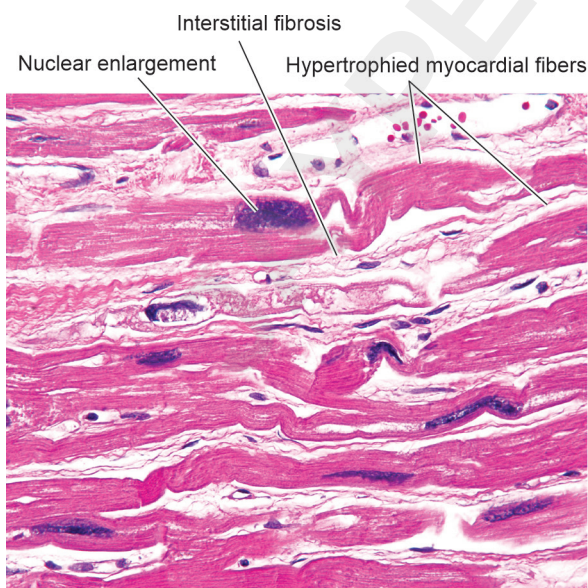


Figure 17.9 Cardiac hypertrophy. Longitudinally sectioned cardiac myocytes are thick with enlarged, hyperchromatic vesicular nuclei and abundant cytoplasm. (Reproduced with permission from *Atlas of Histopathology* by Ivan Damjanov 2012, Jaypee Brothers Medical Publishers Pvt Ltd, New Delhi).

SUMMARY Heart Failure

- **Definition** Heart failure is a condition where the heart is unable to pump sufficient blood to meet the metabolic needs of the body.
- **Causes**
 - ◆ Intrinsic pump failure
 - ◆ Increased pressure or volume overload
 - ◆ Impaired filling
- **Types**
 - ◆ Acute or chronic
 - ◆ Left-sided or right-sided
 - ◆ Backward or forward
- **Left heart failure**
 - ◆ Commonly due to prolonged systemic hypertension
 - ◆ Leads to left ventricular hypertrophy (LVH)
 - ◆ Initially presents as concentric hypertrophy (without dilatation), progresses to eccentric hypertrophy (with dilatation) upon decompensation
- **Right heart failure**
 - ◆ Commonly caused by cor pulmonale or pulmonary heart disease
 - ◆ Results in right ventricular hypertrophy (RVH)
 - ◆ Typically presents as chronic condition with thickened right ventricular wall and often with dilatation

- **Compensation mechanisms**
 - ◆ Cardiac hypertrophy (concentric or eccentric)
 - ◆ Cardiac dilatation
 - ◆ Ultimately, both the left and right heart may show biventricular enlargement

CONGENITAL HEART DISEASE

Congenital heart disease is the abnormality of the heart present from birth. It is the most common and important form of heart disease in the early years of life and is present in approximately 1% of neonates. The incidence is higher in premature infants. The cause of congenital heart disease is unknown in majority of cases. Congenital heart disease is attributed to multifactorial inheritance, involving genes and chromosomes. Other factors which may cause *in utero* fetal injury resulting in congenital malformations of the heart include environmental influence and maternal factors during pregnancy such as her diet, use of medications, heavy alcohol consumption, rubella infection, etc.

CLASSIFICATION Congenital anomalies of the heart may be either *shunts* (left-to-right or right-to-left), or defects causing *obstructions* to flow. However, complex anomalies involving *combinations* of shunts and obstructions are also often present.

A simple classification of important and common examples of these groups is given in **Table 17.2**. Five most common examples are VSD (ventricular septal defect), ASD (atrial septal defect), PDA (patent ductus arteriosus), pulmonary stenosis and tetralogy of Fallot, discussed below.

I. MALPOSITIONS OF THE HEART

Dextrocardia is the condition when the apex of the heart points to the right side of the chest. It may be accompanied by situs inversus, i.e. all other organs of the body are also transposed in a similar way, and thus the heart is in normal position in relation to them. However, isolated dextrocardia is associated with major anomalies of the heart such as transposition of the atria in relation to ventricles, or transposition of the great arteries.

II. SHUNTS (CYANOTIC CONGENITAL HEART DISEASE)

A shunt may be left-to-right side, or right-to-left side of the circulation.

TABLE 17.2 Classification of congenital heart diseases.

I.	MALPOSITIONS OF THE HEART
II.	SHUNTS (CYANOTIC CONGENITAL HEART DISEASE)
	A. <i>Left-to-right shunts (Acyanotic or late cyanotic group)</i>
	1. Ventricular septal defect (VSD), <i>most common</i>
	2. Atrial septal defect (ASD)
	3. Patent ductus arteriosus (PDA)
	B. <i>Right-to-left shunts (Cyanotic group)</i>
	1. Tetralogy of Fallot
	2. Transposition of great arteries
	3. Persistent truncus arteriosus
	4. Tricuspid atresia and stenosis
III.	OBSTRUCTIONS (OBSTRUCTIVE CONGENITAL HEART DISEASE)
	1. Coarctation of aorta
	2. Aortic stenosis and atresia
	3. Pulmonary stenosis and atresia

A. LEFT-TO-RIGHT SHUNTS (ACYANOTIC OR LATE CYANOTIC GROUP)

In conditions where there is shunting of blood from the left-to-right side of the heart, there is volume overload on the right heart producing pulmonary hypertension and right ventricular hypertrophy. At a later stage, the pressure on the right side is higher than on the left side creating late cyanotic heart disease. The important conditions included in this category are described below.

VENTRICULAR SEPTAL DEFECT Ventricular septal defect (VSD) is the most common congenital anomaly of the heart and comprises about 30–40% of all congenital heart diseases. The condition is recognized early in life. The smaller defects often close spontaneously, while larger defects remain patent and produce significant effects.

Depending upon the location of the defect, VSD may be of the following types:

1. In 90% of cases, the defect involves *membranous septum* and is very close to the bundle of His and involves a small membranous part of the interventricular septum, near the aortic and mitral valves (**Fig. 17.10**).
2. The remaining 10% cases have VSD take place in muscular part of the interventricular septum. They can be either inlet VSDs, near the ventricular inlet parts closed to mitral or tricuspid valves, or outlet VSDs, near the outlet part of ventricles, near the aortic (*subaortic*) or pulmonary valves (*subpulmonic*). Inlet VSDs are commonly associated with ASDs.

MORPHOLOGY The *effects* of VSD are produced due to left-to-right shunt at the ventricular level, causing increased right ventricle volume, increased pulmonary flow, increased pulmonary blood flow, and increased volume entering in the left side of the heart. The morphological effects on the heart are as follows:

- i) Volume hypertrophy of the right ventricle.
- ii) Enlargement and hemodynamic changes in the tricuspid and pulmonary valves.
- iii) Endocardial hypertrophy of the right ventricle.
- iv) Pressure hypertrophy of the right atrium.
- v) Volume hypertrophy of the left atrium and left ventricle.
- vi) Enlargement and hemodynamic changes in the mitral and aortic valves.

ATRIAL SEPTAL DEFECT Isolated atrial septal defect (ASD) comprises about 10% of congenital heart diseases. The condition remains unnoticed in infancy and childhood till pulmonary hypertension is induced causing late cyanotic heart disease and right-sided heart failure.

Depending upon the location of the defect, there are 3 types of ASD:

- i) **Fossa ovalis type or ostium secundum type** is the most common form comprising about 90% cases of ASD. The defect is situated in the region of the fossa ovalis (**Fig. 17.11**).
- ii) **Ostium primum type** comprises about 5% of cases of ASD. The defect lies low in the interatrial septum adjacent to atrioventricular valves. There may be cleft in the aortic leaflet of the mitral valve producing mitral insufficiency.
- iii) **Sinus venosus type** accounts for about 5% of ASD cases. The defect is located high in the interatrial septum near the entry of the superior vena cava.

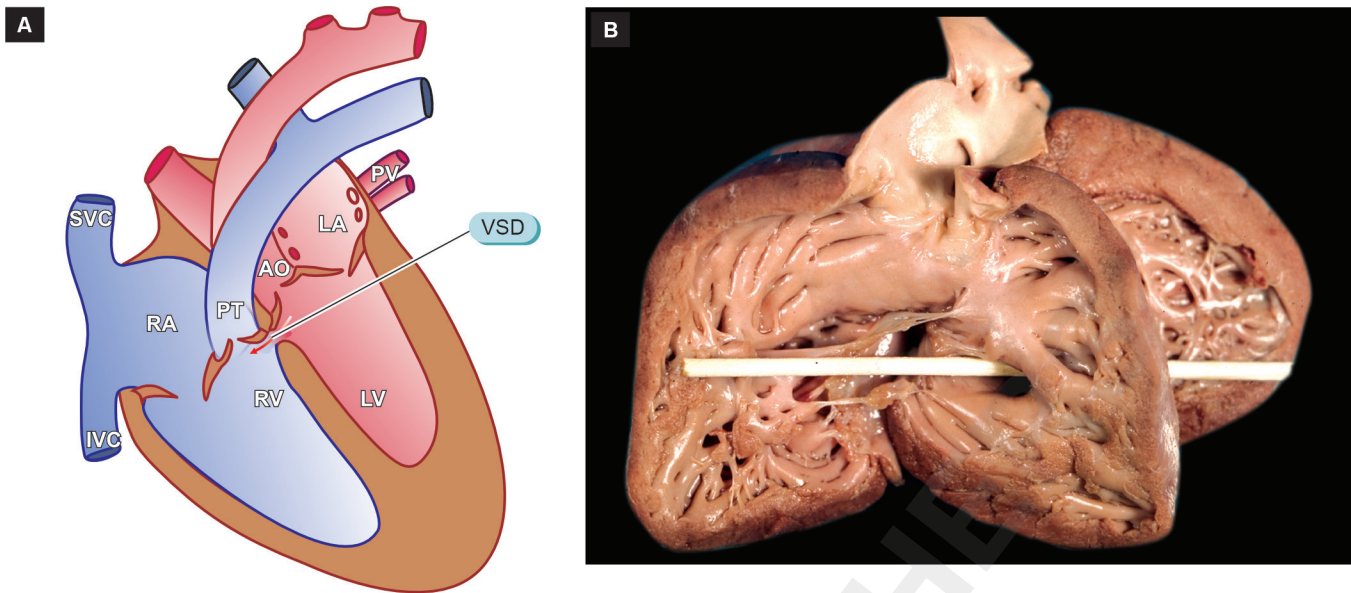


Figure 17.10 Ventricular septal defect. A, Schematic representation. B, The opened up chambers of the heart show a communication in the interventricular septum superiorly (white pipe). (LA, left atrium; LV, left ventricle; AO, aorta; PV, pulmonary valve; PT, pulmonary trunk; RA, right atrium; RV, right ventricle; SVC, superior vena cava; IVC, inferior vena cava; VSD, ventricular septal defect). (Gross image courtesy by Dr Ivan Damjanov, Department of Pathology and Laboratory Medicine, The University of Kansas School of Medicine, Kansas, USA).

MORPHOLOGY The effects of ASD are produced due to left-to-right shunt at the atrial level with increased pulmonary flow. The effects on the heart are:

- i) Volume hypertrophy of the right atrium and right ventricle.
- ii) Enlargement and hemodynamic changes of tricuspid and pulmonary valves.
- iii) Focal or diffuse endocardial hypertrophy of the right atrium and right ventricle.
- iv) Volume atrophy of the left atrium and left ventricle.
- v) Small-sized mitral and aortic orifices.

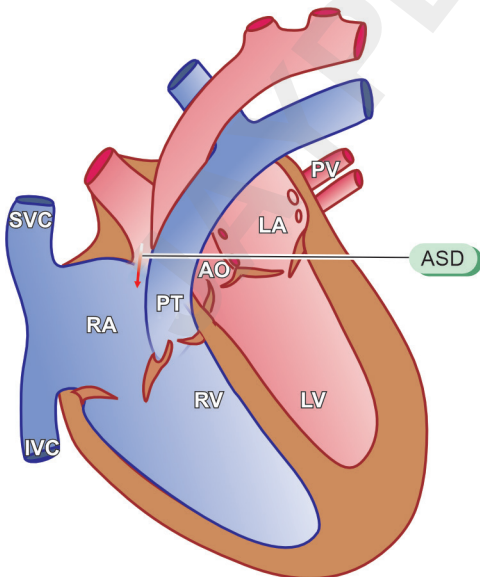


Figure 17.11 Atrial septal defect fossa ovalis type, a schematic representation. (LA, left atrium; LV, left ventricle; PV, pulmonary vein; AO, aorta; PT, pulmonary trunk; RA, right atrium; RV, right ventricle; SVC, superior vena cava; IVC, inferior vena cava; ASD, atrial septal defect).

PATENT DUCTUS ARTERIOSUS (PDA) The ductus arteriosus is a normal vascular connection between the aorta and the bifurcation of the pulmonary artery. Normally, ductus closes functionally within the first or second day of life. Its persistence after 3 months of age is considered abnormal. Prostaglandins, especially PGE₂, maintain the patency of the ductus; continued synthesis of PGE₂ after birth in infants with respiratory distress syndrome is associated with PDA. Thus, inhibition of PGE₂ synthesis by administration of indomethacin causes pharmacologic closure of PDA. PDA constitutes about 10% of congenital malformations of the heart and great vessels. In about 90% of cases, it occurs as an isolated defect, while in the remaining cases it may be associated with other anomalies like VSD, coarctation of aorta and pulmonary or aortic stenosis. A patent ductus may be up to 2 cm in length and up to 1 cm in diameter (**Fig. 17.12**).

MORPHOLOGY The effects of PDA on heart occur due to left-to-right shunt at the level of ductus resulting in increased pulmonary flow and increased volume in the left heart. These effects are:

- i) Volume hypertrophy of the left atrium and left ventricle.
- ii) Enlargement and hemodynamic changes of the mitral and pulmonary valves.
- iii) Enlargement of the ascending aorta.

B. RIGHT-TO-LEFT SHUNTS (CYANOTIC GROUP)

In this group, the blood shunts from right side to the left side of the heart, thereby allowing the entry of poorly oxygenated blood into systemic circulation resulting in *early cyanosis*. The examples described below are not pure shunts, but are combinations of shunts with obstructions; however, these are described here since there is functional shunting of blood from one to the other side of circulation.

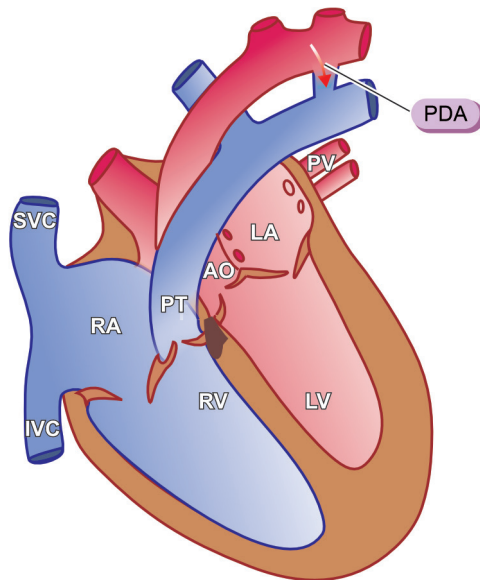
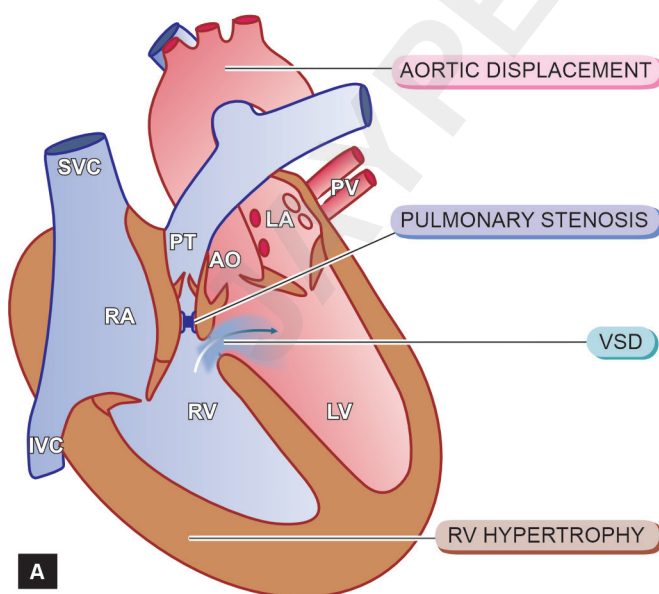


Figure 17.12 Patent ductus arteriosus, a schematic representation. (LA, left atrium; LV, left ventricle; PT, pulmonary trunk; PV, pulmonary vein; AO, aorta; RA, right atrium; RV, right ventricle; SVC, superior vena cava; IVC, inferior vena cava; PDS, patent ductus arteriosus).

TETRALOGY OF FALLOT Tetralogy of Fallot is the most common cyanotic congenital heart disease, found in about 10% of children with anomalies of the heart.

MORPHOLOGY The four features of tetralogy are as under*:
(Fig. 17.13):

- i) Ventricular septal defect (VSD) (*shunt*)
- ii) Displacement of the aorta to right so that it overrides the VSD
- iii) Pulmonary stenosis (*obstruction*)
- iv) Right ventricular hypertrophy



The severity of clinical manifestations is related to two factors—the extent of pulmonary stenosis and the size of VSD. Accordingly, there are two forms of tetralogy: cyanotic and acyanotic.

a) Cyanotic tetralogy Pulmonary stenosis is greater while the VSD is mild; so there is more resistance to the outflow of blood from right ventricle resulting in right-to-left shunt at the ventricular level and cyanosis. The *effects* on the heart are as follows:

- i) Pressure hypertrophy of the right atrium and right ventricle
- ii) Smaller and abnormal tricuspid valve
- iii) Smaller left atrium and left ventricle
- iv) Enlarged aortic orifice

b) Acyanotic tetralogy In this, the VSD is larger, and pulmonary stenosis is mild; so there is mainly left-to-right shunt with increased pulmonary flow and increased volume in the left heart but no cyanosis. The *effects* on the heart are as under:

- i) Pressure hypertrophy of the right ventricle and right atrium
- ii) Volume hypertrophy of the left atrium and left ventricle
- iii) Enlargement of mitral and aortic orifices.

III. OBSTRUCTIONS

(OBSTRUCTIVE CONGENITAL HEART DISEASE)

Congenital obstruction to blood flow may result from obstruction in the aorta due to narrowing of an arterial segment (*coarctation of aorta*), left ventricular outflow obstruction (*aortic stenosis and atresia*), and right ventricular outflow obstruction (*pulmonary stenosis and atresia*).

COARCTATION OF AORTA The word ‘coarctation’ means contracted or compressed. Coarctation of aorta is localized narrowing in any part of aorta, but the constriction is more often just distal to ductus arteriosus (*postductal or adult*), or



Figure 17.13 Tetralogy of Fallot, A, a schematic representation. (LA, left atrium; LV, left ventricle; PT, pulmonary trunk; PV, pulmonary vein; AO, aorta; RA, right atrium; RV, right ventricle; SVC, superior vena cava; IVC, inferior vena cava; PDA, patent ductus arteriosus; VSD, ventricular septal defect). B, Gross features of tetralogy of Fallot. (Image contributed by Dr Sudheer Arava, Professor of Pathology, AIIMS, New Delhi).

*Easy way to remember from acronym *PROVe* = Pulmonary stenosis, Right ventricular hypertrophy, Overriding of aorta, Ventricular septal defect.

occasionally proximal to the ductus arteriosus (*preductal or infantile type*) in the region of transverse aorta:

MORPHOLOGY The two common forms of coarctation of the aorta are postductal (adult) and preductal (infantile) type:

i) Postductal or adult type In this, the obstruction is just distal to the point of entry of ductus arteriosus which is often closed (**Fig. 17.14**). In the stenotic segment, the aorta is drawn in as if a suture has been tied around it. The aorta is dilated on either side of the constriction. The condition is recognized in adulthood, characterized by hypertension in the upper extremities, weak pulses and low blood pressure in the lower extremities, and effects of arterial insufficiency such as claudication and coldness in lower limbs. In time, there is development of collateral circulation between pre-stenotic and post-stenotic arterial branches so that intercostal arteries are enlarged and palpable and may produce erosions on the inner surface of the ribs.

ii) Preductal or infantile type In these cases, the manifestations appear early in life. The narrowing is proximal to the ductus arteriosus which usually remains patent. The narrowing is generally gradual and involves a larger segment of the proximal aorta. There is often associated interatrial septal defect. Preductal coarctation results in right ventricular hypertrophy while the left ventricle is small. Cyanosis develops in the lower half of the body while the upper half remains unaffected since it is supplied by vessels originating proximal to the coarctation. Children with this defect have poor prognosis.

AORTIC STENOSIS AND ATRESIA The most common congenital anomaly of the aorta is *bicuspid aortic valve* which does not have much functional significance but predisposes it to calcification (page 487). Congenital aortic atresia is rare and incompatible with survival. Aortic stenosis may be acquired

(e.g. in rheumatic heart disease, calcific aortic stenosis) or congenital.

MORPHOLOGY Congenital aortic stenosis may be of three types—valvular, subvalvular and supra-valvular.

i) Valvular stenosis In this, the aortic valve cusps are malformed and are irregularly thickened. The aortic valve may have one, two or three maldeveloped cusps.

ii) Subvalvular stenosis In these cases, there is thick fibrous ring under the aortic valve causing subaortic stenosis.

iii) Supra-valvular stenosis This is the most uncommon type. There is fibrous constriction above the sinuses of Valsalva.

In all these cases, there is pressure hypertrophy of the left ventricle and left atrium, and dilatation of the aortic root.

PULMONARY STENOSIS AND ATRESIA Isolated pulmonary stenosis and atresia do not cause cyanosis and hence are included under acyanotic heart diseases.

MORPHOLOGY The features are as under:

Pulmonary stenosis It is the commonest form of obstructive congenital heart disease (7% of all congenital heart diseases). It may occur as a component of the tetralogy of Fallot or as an isolated defect. Pulmonary stenosis is caused by fusion of cusps of the pulmonary valve forming a diaphragm-like obstruction to the outflow of blood from the right ventricle and dilatation of the pulmonary trunk.

Pulmonary atresia In these cases, there is no communication between the right ventricle and lungs so that the blood bypasses the right ventricle through an interatrial septal defect. It then enters the lungs via patent ductus arteriosus.

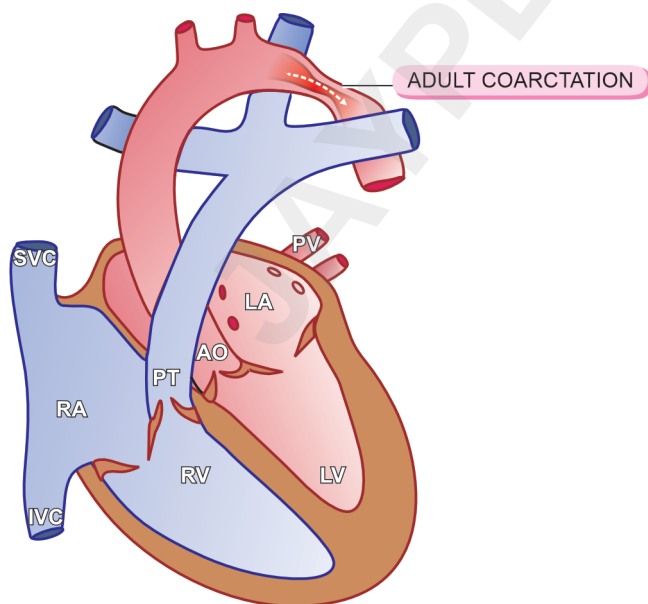


Figure 17.14 Postductal or adult type coarctation of the aorta, a schematic representation. (LA, left atrium; LV, left ventricle; PT, pulmonary trunk; PV, pulmonary vein; AO, aorta; RA, right atrium; RV, right ventricle; SVC, superior vena cava; IVC, inferior vena cava).

SUMMARY Congenital Heart Disease

- **Incidence** Seen in approximately 1% of neonates; higher incidence in premature infants.
- **Causes** Exact cause often unknown; multifactorial inheritance; involves both genetic and environmental factors.
- **Types** Cyanotic and acyanotic congenital heart disease
 - ◆ **Cyanotic heart diseases** Due to right-to-left shunts, resulting in poorly oxygenated blood entering systemic circulation, causing cyanosis (a bluish tint to the skin). Common examples:
 - ◆ **Tetralogy of Fallot** Characterized by four key defects: interventricular septal defect, pulmonary stenosis, right ventricular hypertrophy, and an overriding aorta. The combination of defects results in right ventricular outflow obstruction and right-to-left shunt, causing early cyanosis.
 - ◆ **Transposition of the great arteries** The positions of the pulmonary artery and the aorta are switched, leading to poor oxygenation of blood in circulation.
 - ◆ **Tricuspid atresia** The tricuspid valve is absent, obstructing blood flow from the right atrium to the right ventricle.

- ◆ **Persistent truncus arteriosus** A single arterial trunk arises from the heart, instead of separate pulmonary artery and aorta.
- ◆ **Acyanotic heart diseases** Due to left-to-right shunt; leads to increased pulmonary blood flow and potential late cyanosis. Examples:
 - ◆ **Ventricular septal defect (VSD)** The most common congenital heart disease; involves an opening in the interventricular septum.
Main pathophysiologic effect is left-to-right shunt at the ventricular level causes increased right ventricular volume, increased pulmonary flow, and subsequent volume overload on the left heart.
 - ◆ **Atrial septal defect (ASD)** An opening in the interatrial septum; allows blood to flow between the right and left atria.
Main pathophysiologic effect is left-to-right shunt at the atrial level increases pulmonary flow and right heart volume, potentially leading to late cyanosis due to pulmonary hypertension.
- ◆ **Patent ductus arteriosus (PDA)** The ductus arteriosus, a fetal blood vessel, fails to close after birth.
The effect is persistence of the ductus arteriosus results in a left-to-right shunt, increasing pulmonary flow and volume load on the left heart.
- ◆ **Coarctation of the aorta** A narrowing of the aorta, typically just after the ductus arteriosus, leading to increased blood pressure in the upper body.
The effect is localized narrowing of the aorta causes increased blood pressure in the upper body and decreased circulation to the lower extremities.
- ◆ **Pulmonary stenosis** A narrowing at the pulmonary valve or artery, obstructing blood flow from the right ventricle to the lungs.

ISCHEMIC HEART DISEASE

Ischemic heart disease (IHD) is defined as acute or chronic form of impaired cardiac function arising from imbalance between the myocardial supply and demand for oxygenated blood. Since narrowing or obstruction of the coronary arterial system due to atherosclerosis is the most common cause of myocardial anoxia, the alternate terms '*coronary artery disease (CAD)*' and '*atherosclerotic cardiovascular disease*' are used synonymously with IHD.

Although there is regional variation, worldwide it is estimated that IHD or CAD affects ~3–4% of the population. It is the leading cause of death in high income countries accounting for about a quarter of all deaths, and somewhat lower incidence is observed in low- and middle-income countries. A rising trend in incidence in the countries with increasing urbanization and emerging economies, particularly in South Asia, is attributed to increased consumption of the energy-rich Western diet, and thus higher prevalence of major risk factors for IHD such as obesity, lipid abnormalities, type 2 diabetes mellitus, and hypertension. Men tend to develop IHD earlier than women, although the gap narrows after menopause.

ETIOPATHOGENESIS

IHD is invariably caused by disease affecting coronary arteries, the most prevalent being atherosclerosis accounting for more

than 90% cases, while other causes are responsible for less than 10% cases of IHD. Therefore, it is convenient to consider the etiology of IHD under three broad headings:

- I. Coronary atherosclerosis
- II. Superimposed changes in coronary atherosclerosis
- III. Non-atherosclerotic causes.

I. CORONARY ATHEROSCLEROSIS

Coronary atherosclerosis resulting in 'fixed' obstruction is the major cause of IHD in more than 90% of cases. The general aspects of atherosclerosis, including its etiology, pathogenesis, and the morphological features of atherosclerotic lesions, have already been discussed in detail in Chapter 16 (page 429). Here, a brief account of the specific features pertaining to the pathology of lesions in *atherosclerotic coronary artery disease* is presented here.

1. Distribution Atherosclerotic lesions in coronary arteries are distributed in one or more of the three major coronary arterial trunks, the highest incidence being in the *anterior descending branch of the left coronary (LAD)*, followed in decreasing frequency, by the *right coronary artery (RCA)*, and still less in *circumflex branch of the left coronary (CXA)*. About one-third of cases have *single-vessel disease*, most often involving LAD; another one-third have *two-vessel disease*, and the remainder have *three-major vessel disease*.

2. Location Almost all adults show atherosclerotic plaques scattered throughout the coronary arterial system. However, significant stenotic lesions that may produce chronic myocardial ischemia, show more than 75% (three-fourth) reduction in the cross-sectional area of a coronary artery or its branch. The area of severest involvement is about 3 to 4 cm from the coronary ostia, more often at or near the bifurcation of the arteries, suggesting the role of hemodynamic forces in atherogenesis.

3. Fixed atherosclerotic plaques Atherosclerotic plaques in the coronaries are more often eccentrically located bulging into the lumen from one side (**Fig. 17.15**). Occasionally, there may be concentric thickening of the wall of the artery. Atherosclerosis produces gradual luminal narrowing that may eventually lead to 'fixed' coronary obstruction. The general features of atheroma of

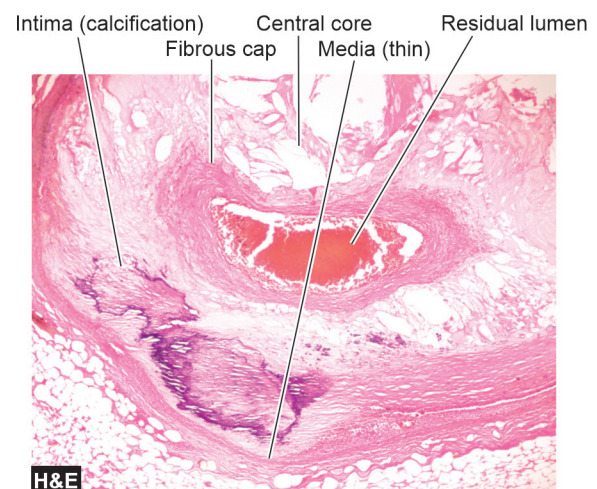


Figure 17.15 Left anterior descending (LAD) coronary artery showing critical narrowing with eccentric luminal obliteration due to atheromatous plaque having a hard sclerotic and calcified core. The residual lumen is reduced to a slit-like.

coronary arteries are similar to those affecting elsewhere in the body and may develop similar complications like calcification, coronary thrombosis, ulceration, hemorrhage, rupture and aneurysm formation (page 430).

II. SUPERIMPOSED CHANGES IN CORONARY ATHEROSCLEROSIS

The complications of *acute coronary syndromes*, which include acute myocardial infarction, unstable angina and sudden ischemic death, are precipitated by certain changes superimposed on a pre-existing fixed coronary atheromatous plaque. These changes are as under:

1. Acute changes in chronic atheromatous plaque Though chronic fixed obstructions are the most frequent cause of IHD, acute coronary episodes are often precipitated by sudden changes in chronic plaques such as plaque hemorrhage, fissuring, or ulceration that result in thrombosis and embolization of atheromatous debris. Acute plaque changes are brought about by factors such as sudden coronary artery spasm, tachycardia, intraplaque hemorrhage and hypercholesterolemia.

2. Coronary artery thrombosis Transmural acute myocardial infarction is often precipitated by partial or complete coronary thrombosis. The initiation of thrombus occurs due to surface ulceration of fixed chronic atheromatous plaque, ultimately causing complete luminal occlusion. The lipid core of plaque is highly thrombogenic. Small fragments of thrombotic material are then dislodged which are embolized to terminal coronary branches and cause microinfarcts of the myocardium.

3. Local platelet aggregation and coronary artery spasm Some cases of acute coronary episodes are caused by local aggregates of platelets on the atheromatous plaque, short of forming a thrombus. The aggregated platelets release vasospastic mediators such as thromboxane A₂ which may probably be responsible for coronary vasospasm in the already atherosclerotic vessel.

III. NON-ATHEROSCLEROTIC CAUSES

Several other coronary lesions may cause IHD, but they together comprise less than 10% of cases. These are as under:

1. Vasospasm Coronary artery vasospasm has been documented to cause near complete occlusion of major coronary arterial trunks in absence of significant atherosclerotic changes, causing angina or myocardial infarction.

2. Stenosis of coronary ostia Coronary ostial narrowing may result from extension of syphilitic aortitis or from aortic atherosclerotic plaques encroaching on the opening.

3. Arteritis Various types of inflammatory involvements of coronary arteries or small branches like in rheumatic arteritis, polyarteritis nodosa, thromboangiitis obliterans (Buerger disease), Takayasu disease, Kawasaki disease, tuberculosis and other bacterial infections may contribute to myocardial damage.

4. Embolism Rarely, emboli originating from elsewhere in the body may occlude the left coronary artery and its branches and produce IHD. The emboli may originate from bland thrombi, or from vegetations of bacterial endocarditis. Rarely, fat embolism and air embolism of coronary circulation may occur.

5. Thrombotic diseases Another infrequent cause of coronary occlusion is from hypercoagulability of the blood such as in shock, polycythemia vera, sickle cell anemia and thrombotic thrombocytopenic purpura.

6. Trauma Contusion of a coronary artery from penetrating injuries may produce thrombotic occlusion.

7. Aneurysms Extension of dissecting aneurysms of the aorta into the coronary artery may produce thrombotic coronary occlusion. Rarely, congenital, mycotic and syphilitic aneurysms may occur in coronary arteries and produce similar occlusive effects.

8. Compression Compression of a coronary from outside by a primary or secondary tumor of the heart may result in coronary occlusion.

9. Cocaine abuse Regular cocaine use by adults is known to be associated with higher risk of heart attack and stroke.

EFFECTS OF MYOCARDIAL ISCHEMIA

Development of lesions in the coronaries is not always accompanied by cardiac disease. Depending upon the suddenness of onset, duration, degree, location and extent of the area affected by myocardial ischemia, the spectrum of changes and clinical features may range from an asymptomatic state at one extreme to the immediate mortality at another end (**Fig. 17.16**):

- I. Asymptomatic state
- II. Angina pectoris (AP)
- III. Acute myocardial infarction (AMI)
- IV. Chronic ischemic heart disease (CIHD)
- V. Sudden cardiac death

The term *acute coronary syndromes* include a triad of acute myocardial infarction, unstable angina and sudden cardiac death.

ANGINA PECTORIS

Angina pectoris is a clinical syndrome of IHD resulting from transient myocardial ischemia. It is characterized by paroxysmal pain in the substernal or precordial region of the chest which is aggravated by an increase in the demand of the heart and relieved by a decrease in the work of the heart. Often, the pain radiates to the left arm, neck, jaw or right arm. It is more common in men past 5th decade of life.

There are three overlapping clinical patterns of angina pectoris with some differences in their pathogenesis:

- i) Stable or typical angina
- ii) Prinzmetal variant angina
- iii) Unstable or crescendo angina

STABLE OR TYPICAL ANGINA This is the most common type. Stable or typical angina is characterized by attacks of chest pain following physical exertion or emotional stress, and the symptoms are relieved by rest. The underlying cause is *chronic stenosing coronary atherosclerosis*, which fails to supply enough blood to the heart muscle during increased workload. During attacks, there is ST segment depression in the ECG due to poor perfusion of the subendocardial region of the left ventricle, but no elevation of cardiac enzymes since there is no irreversible myocardial injury.

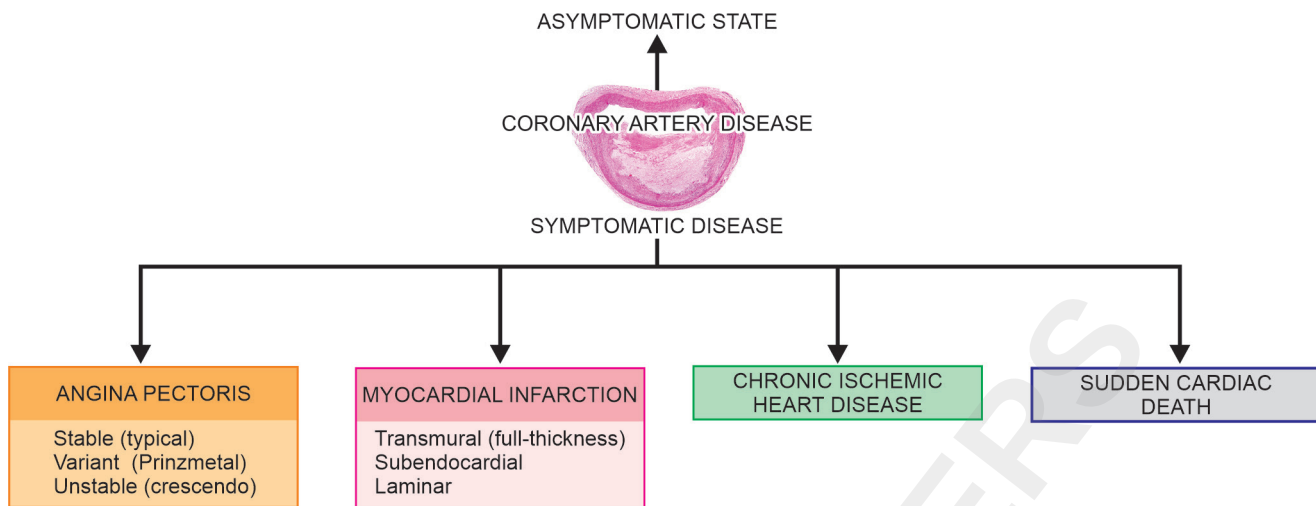


Figure 17.16 Spectrum of coronary ischemic manifestations.

PRINZMETAL VARIANT ANGINA This angina is characterized by pain at rest, unrelated to physical activity. The exact cause is unknown, but it may result from *sudden vasospasm* of a coronary artery, often associated with atherosclerosis or the release of vasoconstrictors from mast cells. ECG shows ST segment elevation due to transmural ischemia. These episodes respond well to vasodilators like nitroglycerin.

UNSTABLE OR CRESCENDO ANGINA Also called ‘pre-infarction angina’ or ‘acute coronary insufficiency’, this is the most serious form. It is characterized by more frequent and prolonged pain, often occurring at rest, and signals impending acute myocardial infarction. Unstable angina is distinguished from acute MI by ECG—MI shows ST segment elevation, while unstable angina may have non-ST segment elevation MI; in the latter cases, cardiac biomarkers (like troponin) are elevated but there is no ST segment elevation. *Multiple factors* contribute to unstable angina, such as stenosing coronary atherosclerosis, complicated plaques (thrombosis, hemorrhage, rupture, ulceration), platelet thrombi, and coronary vasospasm. These lesions are often in a branch of a major coronary artery, with collateral vessels preventing infarction.

ACUTE MYOCARDIAL INFARCTION

Acute myocardial infarction (AMI) is the most serious complication of coronary artery disease. Many patients die within the first few hours of onset, while the remainder suffer from impaired cardiac function. A key factor that can reduce myocardial damage is the development of collateral circulation over time. Regular, planned exercise encourages good collateral circulation and improves cardiac performance.

INCIDENCE AMI accounts for 10–25% of all deaths, mostly outside hospitals. There is decline in-hospital mortality from 10% to ~5%. In view of dominant role of atherosclerosis in its etiology, the incidence of AMI closely correlates with the prevalence of atherosclerosis in a geographic region.

Age AMI can occur at any age but is more common in the elderly. About 5% of heart attacks occur in people under 40, especially those with major risk factors for atherosclerosis, such as hypertension, diabetes, smoking, and dyslipidemia including familial hypercholesterolemia.

Sex Males are at a significantly higher risk of AMI throughout life compared to females. Women of reproductive age have a low risk, likely due to some protective influence of estrogen. The use of oral contraceptives increases the risk of AMI. After menopause, the gender difference gradually decreases, but the incidence of AMI in women never matches that of men of the same age.

ETIOPATHOGENESIS Severe coronary atherosclerosis (over 75% narrowing of lumen) of one or more major coronary arteries is found in about 90% of AMI cases in autopsy or angiographic studies. Key factors in development of acute AMI are as under:

1. Myocardial ischemia Myocardial ischemia results from one or more of the following:

- Reduced coronary blood flow, e.g. in coronary artery disease or shock.
- Increased myocardial demand, e.g. during exercise or emotional stress.
- Heart hypertrophy without increased coronary blood flow, as in hypertension or valvular heart disease.

2. Role of platelets Rupture of an atherosclerotic plaque exposes the subendothelial collagen to platelets which undergo aggregation, activation and release reaction. These events contribute to the build-up of the platelet mass that may disseminate as emboli or initiate thrombosis.

3. Acute plaque rupture In general, slowly-developing coronary ischemia from severe coronary atherosclerosis of high-grade may not cause AMI, but may produce episodes of angina pectoris. However, acute complications in coronary atherosclerotic plaques in the form of superimposed coronary thrombosis due to plaque rupture and plaque hemorrhage are frequently encountered in cases of AMI:

- Superimposed coronary thrombosis* due to disruption of plaque is seen in about half the cases of AMI. Infusion of intracoronary fibrinolytics in the first half an hour of development of acute MI in such cases restores blood flow in the blocked vessel in majority of cases.
- Intramural hemorrhage* is found in about one-third cases of AMI.

Plaque hemorrhage and thrombosis may occur together in some cases.

4. Non-atherosclerotic causes About 10% of AMI cases are due to non-atherosclerotic factors, such as coronary vasospasm, arteritis, coronary ostial stenosis, embolism, thrombotic diseases, trauma, or external compression, as already described.

TYPES OF INFARCTS Infarcts have been classified in several ways by physicians and pathologists:

1. According to the anatomic region of the left ventricle involved, they are called anterior, posterior (inferior), lateral, septal and circumferential, and their combinations like anterolateral, posterolateral (or inferolateral) and anteroseptal.

2. According to the degree of thickness of the ventricular wall involved, infarcts are of two types (**Fig. 17.17, Table 17.3**):

i) **Transmural (full thickness) infarcts** are the most common type seen in 95% cases. Critical coronary narrowing (more than 75% compromised lumen) is of great significance in causing such infarcts. Atherosclerotic plaques with superimposed thrombosis and intramural hemorrhage are significant in about 90% cases, and non-atherosclerotic causes in the remaining 10% cases.

ii) **Subendocardial (laminar) infarcts** have their genesis in reduced coronary perfusion due to coronary atherosclerosis but without critical stenosis (luminal compromise less than 75% of luminal diameter), aortic stenosis or hemorrhagic shock. This is because subendocardial myocardium is normally least well perfused by coronaries, and thus is more vulnerable to any reduction in the coronary flow. Superimposed coronary thrombosis is frequently encountered in these cases too, and hence the beneficial role of fibrinolytic treatment in such patients also.

3. According to the age of infarcts, they are of two types:

i) Newly formed infarcts are called *acute, recent or fresh*.

ii) Advanced infarcts are called *old, healed or organized infarcts*.

LOCATION OF INFARCTS Infarcts are most frequently located in the left ventricle. Right ventricle is less susceptible to infarction due to its thin wall, having less metabolic requirements, and is thus adequately nourished by the thebesian vessels. Atrial infarcts, whenever present, are more often in the right atrium, usually accompanying the infarct of the left ventricle. The left atrium is relatively protected from infarction because it is supplied by oxygenated blood in the left atrial chamber.

The region of infarction depends upon the area of obstructed blood supply by one or more of the three coronary arterial trunks. Accordingly, there are three regions of myocardial infarction (**Fig. 17.18**):

1. **Stenosis of the left anterior descending coronary artery (LAD)** is the most common (40–50%). The region of infarction is the anterior part of the left ventricle including the apex and the anterior two-thirds of the interventricular septum.

2. **Stenosis of the right coronary artery (RCA)** is the next most frequent (30–40%). It involves the posterior part of the left ventricle and the posterior one-third of the interventricular septum.

3. **Stenosis of the left circumflex coronary artery (CXA)** is seen least frequently (15–20%). Its area of involvement is the lateral wall of the left ventricle.

MORPHOLOGY The gross and microscopic changes in the myocardial infarction vary according to the age of the infarct and are therefore described sequentially (**Table 17.4**).

Grossly, most infarcts occur singly and vary in size from 4 to 10 cm. As explained above, they are found most often in the left ventricle. Less often, there are multifocal lesions. The transmural infarcts, which involve the entire thickness of the ventricular wall, usually have a thin rim of preserved subendocardial myocardium which is perfused directly by the blood in the ventricular chamber. The subendocardial infarcts which affect the inner subendocardial half of the

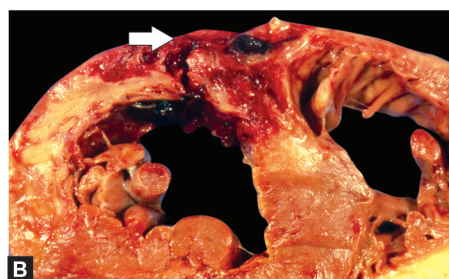
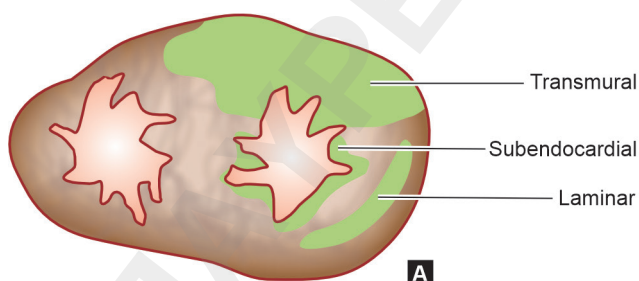


Figure 17.17 A, Diagrammatic representation of extent of myocardial infarction in the depth of myocardium. B, Cross section of the heart having transmural infarct of left ventricle showing ruptured ventricular wall (arrow). (Gross image courtesy by Dr Ivan Damjanov, Department of Pathology and Laboratory Medicine, The University of Kansas School of Medicine, Kansas, USA).

TABLE 17.3 Contrasting features of subendocardial and transmural infarcts.

FEATURE	TRANSMURAL INFARCT	SUBENDOCARDIAL INFARCT
1. Definition	Full-thickness, solid	Inner third to half, patchy
2. Frequency	Most frequent (95%)	Less frequent
3. Distribution	Specific area of coronary supply	Circumferential
4. Pathogenesis	>75% coronary stenosis	Hypoperfusion of inner myocardium
5. Coronary thrombosis	Common	Rare
6. Epicarditis	Common	None

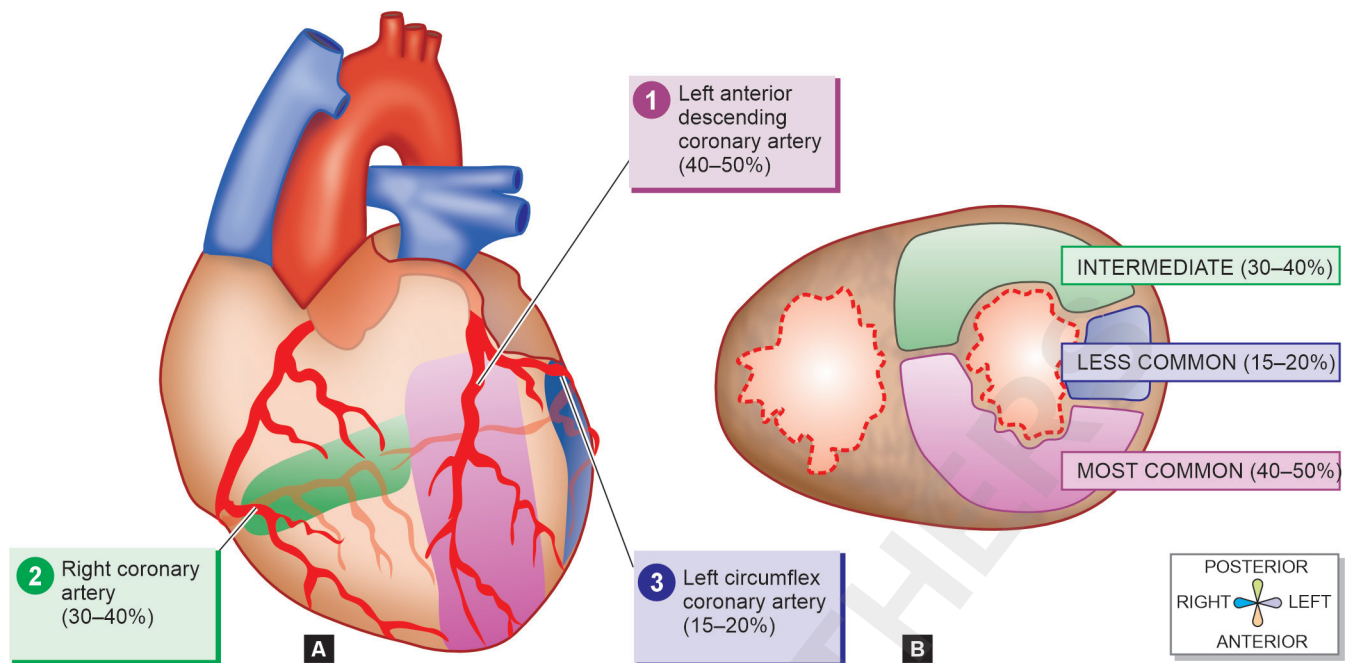


Figure 17.18 Common locations and the regions of involvement in myocardial infarction. The figure shows region of myocardium affected by stenosis of three respective coronary trunks in descending order shown as: 1) left anterior descending coronary, 2) right coronary and 3) left circumflex coronary artery. A, as viewed from anterior surface. B, as viewed on transverse section at the apex of the heart.

myocardium produce less well-defined gross changes than the transmural infarcts. The sequence of macroscopic changes in all myocardial infarcts is as under:

1) *In 6 to 12 hours old infarcts*, no striking gross changes are discernible except that the affected myocardium is slightly paler and drier than normal. However, the early infarcts (3 to 6 hours old) can be detected by histochemical staining for *dehydrogenases* on unfixed slices of the heart. This consists of immersing a slice of unfixed heart in the solution of triphenyl tetrazolium chloride (TTC) which imparts red brown color to the normal heart muscle, while the area of infarcted muscle fails to stain due to lack of dehydrogenases.

Another stain for viability of cardiac muscle is nitro blue tetrazolium (NBT) dye which imparts blue color to unaffected cardiac muscle while infarcted myocardium remains unstained.

2) *By about 24 hours*, the infarct develops cyanotic, red purple, blotchy areas of hemorrhage due to stagnation of blood.

3) *During the next 48 to 72 hours*, the infarct develops a yellow border due to neutrophilic infiltration and thus becomes more well-defined.

4) *In 3-7 days*, the infarct has hyperemic border while the center is yellow and soft.

TABLE 17.4 Sequential pathologic changes in myocardial infarction.

TIME	GROSS CHANGES	LIGHT MICROSCOPY
FIRST WEEK		
0-6 hours	No change or pale; TTC/NBT test negative in infarcted area	No change; stretching and waviness of fibers
6-12 hours	No change or pale; TTC/NBT test negative in infarcted area	Coagulative necrosis begins; neutrophilic infiltration begins; edema and hemorrhages present
24 hours	Cyanotic red-purple area of hemorrhage	Coagulative necrosis progresses; marginal neutrophilic infiltrate
48-72 hours	Pale, hyperemic	Coagulative necrosis complete, neutrophilic infiltrate well developed
3rd-7th day	Hyperemic border, center yellow and soft	Neutrophils gradually disappear, beginning of resorption of necrosed fibers by macrophages, onset of fibrovascular response
SECOND WEEK		
10th day	Red-purple periphery	Most of the necrosed muscles in a small infarct are removed; fibrovascular reaction more prominent; pigmented macrophages, eosinophils, lymphocytes, plasma cells present
14th day	—	Necrosed muscle is mostly removed; neutrophils disappear; fibrocollagenous tissue at the periphery
THIRD WEEK		
—	—	Necrosed muscle fibers from larger infarcts removed; more ingrowth of fibrocollagenous tissue
FOURTH TO SIXTH WEEK		
—	Thin, gray-white, hard, shrunken fibrous scar	Increased fibrocollagenous tissue, decreased vascularity; fewer pigmented macrophages, lymphocytes and plasma cells

(TTC, triphenyl tetrazolium chloride; NBT, nitro blue tetrazolium).

5) By 10 days, the periphery of the infarct appears reddish purple due to growth of granulation tissue. With the passage of time, further healing takes place; the necrotic muscle is resorbed, and the infarct shrinks and becomes pale grey.

6) By the end of 6 weeks, the infarcted area is replaced by a thin, gray-white, hard, shrunken fibrous scar which is well developed in about 2 to 3 months. However, the time taken by an infarct to heal by fibrous scar may vary depending upon the size of the infarct and adequacy of collateral circulation (Fig. 17.19).

Microscopically, the changes are similar in both transmural and subendocardial infarcts. As elsewhere in the body, myocardial ischemia induces *ischemic coagulative necrosis* of the myocardium which eventually heals by fibrosis. However, in myocardial infarction, following time-related sequential light microscopic changes are observed (Fig. 17.20):

1. First week The progression of changes takes place as follows:

i) In the first 6 hours after infarction, usually no detectable histologic change is observed in routine light microscopy. However, some investigators have described stretching and waviness of the myocardial fibers within one hour of the onset of ischemia.

ii) After 6 hours, there is the appearance of some edema fluid between the myocardial fibers. The muscle fibers at the margin of the infarct show vacuolar degeneration called *myocytolysis*.

iii) By 12 hours, coagulative necrosis of the myocardial fibers sets in, and neutrophils begin to appear at the margin of the infarct. Coagulative necrosis of cardiac fibers is characterized by loss of striation and intense eosinophilic, hyaline appearance and may show nuclear changes like karyolysis, pyknosis and karyorrhexis. Hemorrhages and edema are present in the interstitium.



Figure 17.19 Myocardial infarction, healed. Cross section of the left heart at the base shows grey-white area of the anteroseptal myocardium due to healed fibrous scarring (arrow) while rest of the myocardium has brown color (Courtesy by Dr Ivan Damjanov, Department of Pathology and Laboratory Medicine, The University of Kansas School of Medicine, Kansas, USA).

iv) During the first 24 hours, coagulative necrosis progresses further as evidenced by shrunken eosinophilic cytoplasm and pyknosis of the nuclei. The neutrophilic infiltrate at the margins of the infarct is slight (Fig. 17.20, A).

v) During the first 48–72 hours, coagulative necrosis is complete with loss of nuclei. The neutrophilic infiltrate is well developed and extends centrally into the interstitium (Fig. 17.20, B).

vi) In 3–7 days, neutrophils are necrosed and gradually disappear. The process of resorption of necrosed muscle fibers by macrophages begins. Simultaneously, proliferation of capillaries and fibroblasts starts from the infarct margins (Fig. 17.20, C).

vii) During the first 48–72 hours, coagulative necrosis is complete with loss of nuclei. The neutrophilic infiltrate is well developed and extends centrally into the interstitium (Fig. 17.20, B).

viii) In 3–7 days, neutrophils gradually disappear. The process of resorption of necrosed muscle fibers by macrophages begins. Simultaneously, there is proliferation of capillaries and fibroblasts from the margins of the infarct (Fig. 17.20, C).

2. Second week The changes are as under:

i) By the 10th day, most of the necrosed muscle at the periphery of infarct is removed. The fibrovascular reaction at the margin of infarct is more prominent. Many pigmented macrophages containing yellow-brown lipofuscin (derived from breakdown of myocardial cells) and golden-brown hemosiderin (derived from lysed erythrocytes in hemorrhagic areas) are seen. Besides, a few other inflammatory cells like eosinophils, lymphocytes and plasma cells are also present.

ii) By the end of the 2nd week, most of the necrosed muscle in small infarcts is removed, neutrophils have almost disappeared, and newly laid collagen fibers replace the periphery of the infarct.

3. Third week Necrosed muscle fibers from larger infarcts continue to be removed and replaced by ingrowth of newly formed collagen fibers. Pigmented macrophages as well as lymphocytes and plasma cells are prominent while eosinophils gradually disappear.

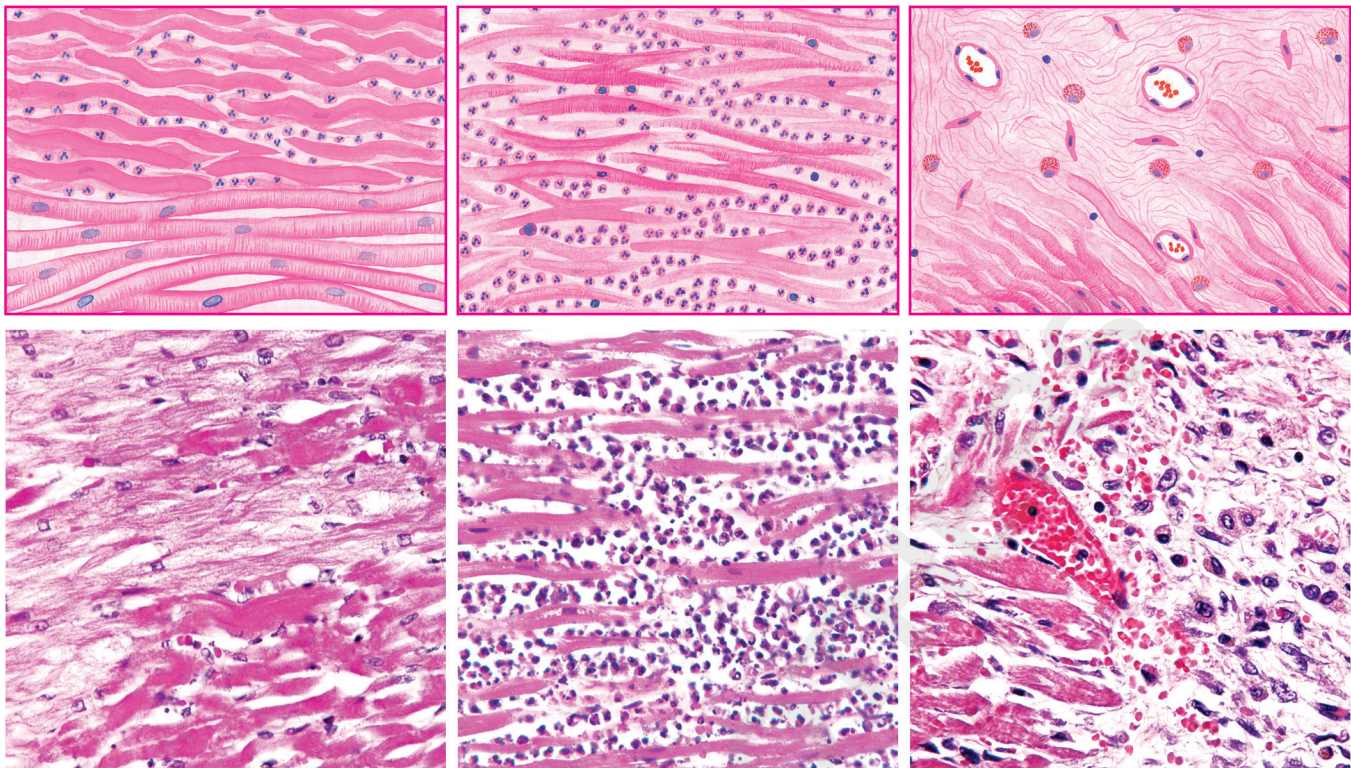
4. Fourth to sixth week With further removal of necrotic tissue, there is an increase in collagenous connective tissue, decreased vascularity and fewer pigmented macrophages, lymphocytes and plasma cells. Thus, at the end of 6 weeks, a contracted fibrocollagenous scar with diminished vascularity is formed (Fig. 17.21). The pigmented macrophages may persist for a long duration in the scar, sometimes for years.

A summary of the sequence of gross and microscopic changes in myocardial infarction of varying duration is presented in Table 17.4.

SALVAGE IN EARLY INFARCTS AND REPERFUSION INJURY

In vast majority of cases of acute MI, occlusive coronary artery thrombosis has been demonstrated superimposed on fibrofatty plaque. The ischemic injury to myocardium is reversible if perfusion is restored within the first 30 minutes of onset of infarction, failing which irreversible ischemic necrosis of myocardium sets in. The salvage in early infarcts can be achieved by the following interventions:

1. Institution of *thrombolytic therapy* with thrombolytic agents such as streptokinase and tissue plasminogen activator (door-to-needle time ≤ 30 minutes).



A, CHANGES DURING THE FIRST 24 HOURS

B, CHANGES DURING THE FIRST 48-72 HOURS

C, CHANGES BY THE END OF FIRST WEEK

Figure 17.20 Sequence of light microscopic changes in myocardial infarction. A, Changes after around 20 hours of occlusion of the coronary artery, there is loss of eosinophilia of infarcted myocytes and infiltration by a few neutrophils. B, Within 48–72 hours, neutrophilic infiltrates dominate the infarcted myocardium. C, At the end of one week after infarction, there is infiltration of macrophages, proliferation of new capillaries and young fibroblasts. (Photomicrographs reproduced with permission from *Atlas of Histopathology* by Ivan Damjanov 2012, Jaypee Brothers Medical Publishers Pvt Ltd, New Delhi).

2. Percutaneous transluminal coronary angioplasty (PTCA).
3. Coronary artery stenting.
4. Coronary artery bypass surgery.

However, late attempts at reperfusion are fraught with the risk of ischemic reperfusion injury (page 40). Further myonecrosis during reperfusion occurs due to rapid influx of calcium ions and generation of toxic oxygen free radicals.

Grossly, the myocardial infarct following reperfusion injury appears *hemorrhagic* rather than pale.

Microscopically, cardiac fibers show *contraction band necrosis* which are transverse and thick eosinophilic bands (**Fig. 17.22**).

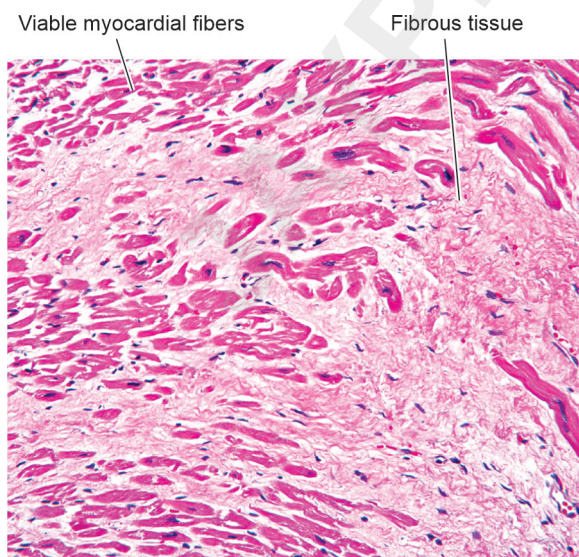


Figure 17.21 Three months after myocardial infarct. The infarcted myocardium has been largely replaced by fibrous tissue. (Reproduced with permission from *Atlas of Histopathology* by Ivan Damjanov 2012, Jaypee Brothers Medical Publishers Pvt Ltd, New Delhi).

CHANGES IN EARLY INFARCTS By special techniques such as electron microscopy, chemical and histochemical studies, irreversible cellular changes can be demonstrated in early infarcts, before detectable light microscopic alterations appear. However, this is not very useful in clinical diagnosis. Only after the myocardial necrosis, certain serum enzymes may be elevated in blood which can be useful in clinical diagnosis.

DIAGNOSIS The diagnosis of acute MI is based on three types of features—clinical features, ECG changes, and serum enzyme determinations.

1. Clinical features Typically, AMI has a sudden onset. The following clinical features usually characterize a case of acute MI.

i) **Pain** Usually sudden, severe, crushing and prolonged, substernal or precordial in location, unrelieved by rest or nitroglycerin, often radiating to one or both the arms, neck and back.

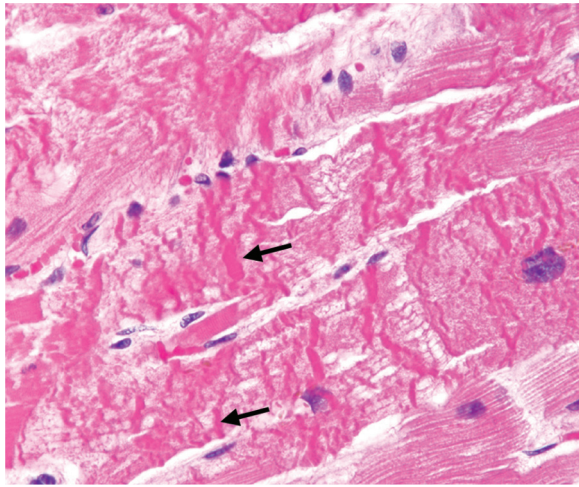


Figure 17.22 Reperfusion of myocardial infarct. Early reperfusion of the infarct saves some myocardial fibers while some other cells undergo contraction band necrosis (arrows). (Reproduced with permission from *Atlas of Histopathology* by Ivan Damjanov 2012, Jaypee Brothers Medical Publishers Pvt Ltd, New Delhi).

- ii) **Indigestion** Pain is often accompanied by epigastric or substernal discomfort interpreted as 'heartburn' with nausea and vomiting.
- iii) **Apprehension** The patient is often terrified, restless and apprehensive due to great fear of death.
- iv) **Shock** Systolic blood pressure is below 80 mm Hg; lethargy, cold clammy limbs, peripheral cyanosis, weak pulse, tachycardia or bradycardia are often present.
- v) **Oliguria** Urine flow is usually less than 20 mL per hour.
- vi) **Low grade fever** Mild rise in temperature occurs within 24 hours and lasts up to one week, accompanied by leukocytosis and elevated ESR.
- vii) **Acute pulmonary edema** Some cases develop severe pulmonary congestion due to left ventricular failure and develop suffocation, dyspnea, orthopnea and bubbling respiration.

2. ECG changes The ECG changes are one of the most important parameters. Most characteristic ECG change is ST segment elevation in AMI (termed as STEMI); other changes include T wave inversion and appearance of wide deep Q waves (**Fig. 17.23**).

3. Serum cardiac biomarkers Certain proteins and enzymes are released into the blood from necrotic heart muscle after AMI. Measurement of their levels in serum is helpful in making

a diagnosis and plan management. Rapid assay of some more specific cardiac proteins is available rendering the estimation of non-specific estimation of SGOT of historical importance only in current practice. Important myocardial markers in use nowadays are as under (**Fig. 17.24**):

- i) **Creatine phosphokinase (CK) and CK-MB.** CK has three forms:
 - a) CK-MM is derived from skeletal muscle.
 - b) CK-BB is derived from the brain and lungs.
 - c) CK-MB mainly from cardiac muscles and insignificant amount from extracardiac tissue.

Thus, total CK estimation lacks specificity while elevation of CK-MB isoenzyme is considerably specific for myocardial damage. CK-MB has 2 further forms: CK-MB2 is the myocardial form, while CK-MB1 is extracardiac form. A ratio of CK-MB2:CK-MB1 more than 1.5 is highly sensitive for the diagnosis of AMI after 4–6 hours of onset of myocardial ischemia. CK-MB disappears from blood by 48 hours.

- ii) **Lactate dehydrogenase (LDH)** Total LDH estimation also lacks specificity since this enzyme is present in various tissues besides myocardium such as in skeletal muscle, kidneys, liver, lungs and red blood cells. However, like CK, LDH too has two isoforms of which LDH-1 is myocardial-specific. Estimation of ratio of LDH-1:LDH-2 above 1 is reasonably helpful in making a diagnosis. LDH levels begin to rise after 24 hours, reach peak in 3 to 6 days and return to normal in 14 days.

- iii) **Cardiac-specific troponins (cTn)** Immunoassay of cTn as a serum cardiac marker has rendered LDH estimation obsolete. Troponins are contractile muscle proteins present in human cardiac and skeletal muscle, but cardiac troponins are specific for myocardium. There are two types of cTn:

- a) cardiac troponin T (cTnT)
- b) cardiac troponin I (cTnI)

Both cTnT and cTnI are found in extremely low concentration in the serum of healthy individuals that can be detected by high-sensitivity assay. But after myocardial injury, their levels rise very high around the same time when CK-MB is elevated (i.e. after 4–6 hours). Both troponin levels remain high for much longer duration; cTnI for 7–10 days and cTnT for 10–14 days.

- iv) **Myoglobin** Though myoglobin is the first cardiac marker to be elevated after myocardial infarction, it lacks cardiac specificity and is excreted in the urine rapidly. Its levels, thus, return to normal within 24 hours of attack of acute MI.

4. Other supportive laboratory tests In addition to serum cardiac biomarkers, a few other laboratory tests either indicate

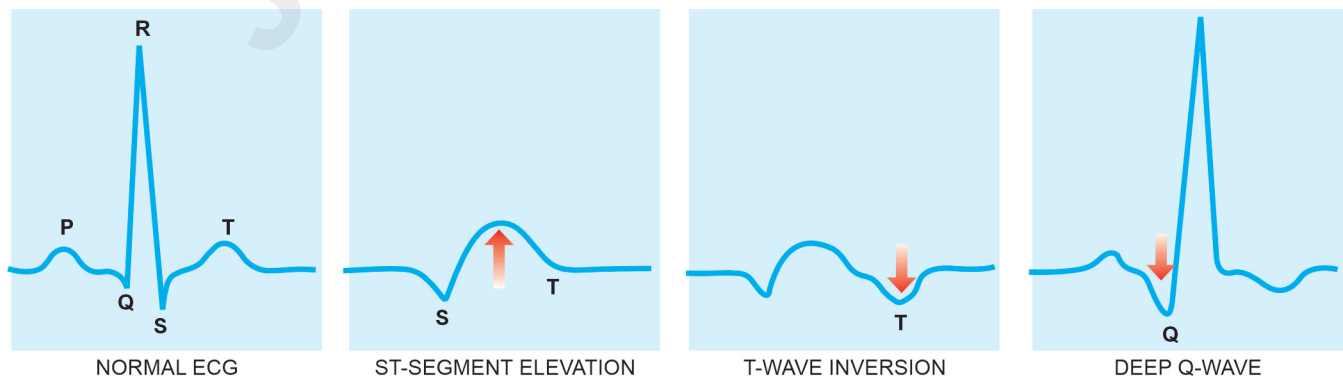


Figure 17.23 Some common ECG changes in acute myocardial infarction.

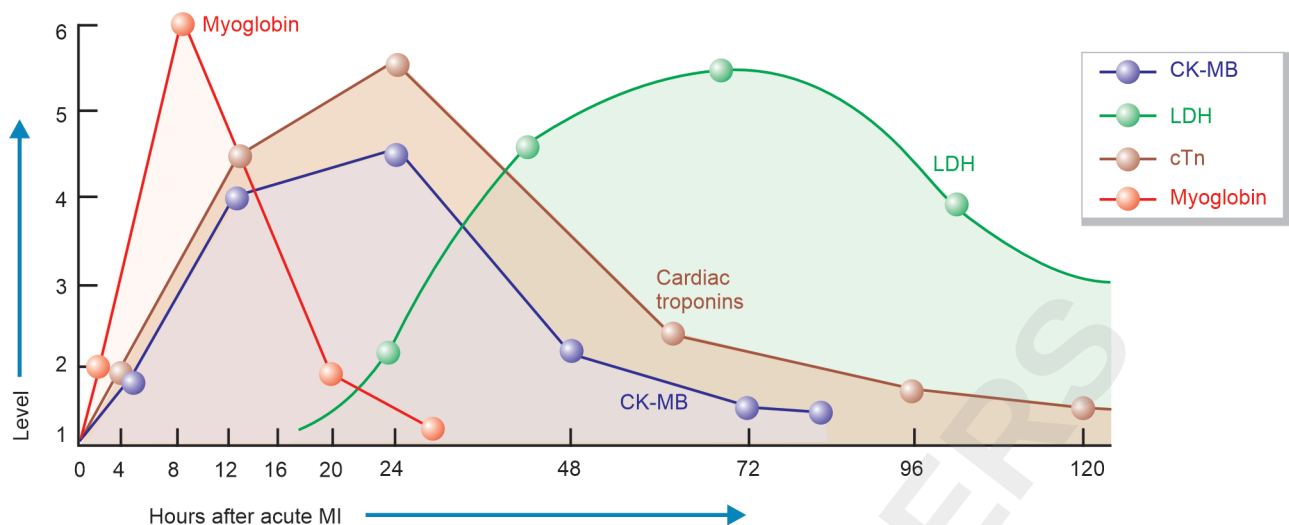


Figure 17.24 Time course of serum cardiac markers for the diagnosis of acute MI.

myocardial ischemic injury or are supportive of susceptibility to acute MI in a patient:

- Polymorphonuclear leukocytosis* is a nonspecific reaction to myocardial damage, appearing within a few hours after coronary ischemia and persists for up to one week.
- ESR* rises slowly after myocardial injury and peaks in a week after ischemia.
- Lipid profile* with measurements of various lipid fractions in the blood.
- Elevated CRP* in serum is a sensitive and independent risk marker for future cardiovascular events.
- Urine analysis includes microalbuminuria* for evidence of diabetes mellitus and renal disease.
- Serum creatinine* for renal disease.
- Glycosylated hemoglobin* estimation for control of diabetes mellitus.

COMPLICATIONS Following an attack of acute MI, only 10–20% cases do not develop major complications and recover. The remainder 80–90% of cases develop one or more major complications, some of which are fatal. The important complications which may develop following acute MI may be early or late:

Early complications These complications develop in the initial period of an episode of AMI and include the following:

- Arrhythmias** Arrhythmias (or abnormalities in the normal cardiac rhythm) are the most common complication in AMI. These occur due to ischemic injury or irritation to the conduction system, resulting in abnormal rhythm. Other causes of arrhythmia include leakage of K^+ from ischemic muscle cells and increased concentration of lactate and free fatty acids in the tissue fluid. Arrhythmias may be in the form of sinus tachycardia or sinus bradycardia, atrial fibrillation, premature systoles, and the most serious ventricular fibrillation responsible for many sudden cardiac deaths.
- Cardiogenic shock** About 10% of patients with AMI develop cardiogenic shock characterized by hypotension with systolic blood pressure of 80 mm Hg or less for many days. Shock may be accompanied by peripheral circulatory failure, oliguria, and mental confusion.
- Cardiac rupture** Rupture of the heart occurs in up to 5% of cases of AMI and results in death. Rupture occurs most often from

the infarcted ventricular wall into the pericardial cavity, causing hemopericardium and tamponade. Other sites of rupture are through the interventricular septum and rupture of a papillary muscle in the infarct of the left ventricle. Rupture at any of these sites occurs usually in the first week and is often fatal.

Delayed complications Following complications may develop after the patient is still recovering or has recovered after AMI:

- Congestive heart failure** About half of the patients with AMI develop right ventricular failure, left ventricular failure, or combined failure, i.e. CHF. CHF is responsible for about 40% of deaths from AMI. If the patient survives, healing may restore normal cardiac function, but in some cases, CHF may persist and require regular treatment later.
- Mural thrombosis and thromboembolism** The incidence of thromboembolism from intracardiac thrombi and from thrombosis in the leg veins is 15–45% in cases of AMI and is the major cause of death in 12% of cases. Mural thrombosis in the heart develops due to involvement of the endocardium and sub-endocardium in the infarct and due to slowing of the heart rate. Mural thrombi often form thromboemboli. Another source of thromboemboli is the venous thrombosis in the leg veins due to prolonged bed rest. Thromboemboli from either source may cause occlusion of the pulmonary, renal, mesenteric, splenic, pancreatic or cerebral arteries and cause infarcts in these organs.
- Cardiac aneurysm** Another 5% of patients with AMI develop aneurysm, often of the left ventricle. It occurs in healed infarcts through thin, fibrous, non-elastic scar tissue. Cardiac aneurysms impair the function of the heart and are the common sites for mural thrombi. Rarely, calcification of the wall of an aneurysm may occur.
- Pericarditis** Sterile pericarditis appearing on about the second day is common over transmural infarcts. It is characterized by fibrinous pericarditis and may be associated with pericardial effusion. Often, it is of no functional significance and resolves spontaneously.
- Post-myocardial infarction syndrome** About 3–4% of patients who had AMI develop post-myocardial infarction syndrome or Dressler syndrome subsequently. It usually occurs 1–6 weeks after the attack of AMI. It presents with sterile pericarditis with pleuritis and pneumonitis. The symptoms are mild and spontaneously disappear on their own in a few weeks. The exact pathogenesis

of this syndrome is not known. It may be due to an autoimmune reaction as evidenced by circulating anti-heart antibodies in the serum of these patients. But these antibodies are also present in some patients with acute MI who do not develop this syndrome.

CHRONIC ISCHEMIC HEART DISEASE

Chronic ischemic heart disease, ischemic cardiomyopathy or myocardial fibrosis, are the terms used for focal or diffuse fibrosis in the myocardium characteristically found in elderly patients of progressive IHD. Such small areas of fibrous scarring are commonly found in the heart of patients who have history of episodes of angina and attacks of MI some years back. These usually develop CHF over a period of years due to progression of lesions and cardiac decompensation. Occasionally, serious cardiac arrhythmias or infarction may supervene and cause death.

ETIOPATHOGENESIS In majority of cases, coronary atherosclerosis is the cause for progressive ischemic myocardial damage and replacement by myocardial fibrosis. A small percentage of cases may result from other causes such as emboli, coronary arteritis and myocarditis, coronary artery spasm, coronary dissection, or cocaine abuse.

The mechanism of development of myocardial fibrosis can be explained as under:

- i) Myocardial fibrosis represents healing of minute infarcts involving small, scattered groups of myocardial fibers.
- ii) An alternate concept of the development of myocardial fibrosis is healing of minute areas of focal myocytolysis, the myocardial fibers in a small area undergo slow degeneration due to myocardial ischemia. These fibers lose their myofibrils, but nuclei remain intact. These foci are infiltrated by macrophages and eventually are replaced by proliferating fibroblasts and collagen.

MORPHOLOGY *Grossly*, the heart may be normal in size or hypertrophied. The left ventricular wall generally shows small gray-white fibrosis foci of fibrosis in the background of normal brown myocardium. Healed scars of previous MI may be present. Valves of the left heart may be distorted, thickened and show calcification. Coronary arteries invariably show moderate to severe atherosclerosis.

Microscopically, the characteristic features are as follows (Fig. 17.25):

- i) There are scattered areas of diffuse myocardial fibrosis, especially around the small blood vessels in the interstitial tissue of the myocardium.
- ii) Intervening single fibers and groups of myocardial fibers show variation in fiber size and foci of myocytolysis.
- iii) Areas of brown atrophy of the myocardium may also be present.
- iv) Coronary arteries show atherosclerotic plaques and may have complicated lesions in the form of superimposed thrombosis.

SUDDEN CARDIAC DEATH

Sudden cardiac death (SCD) is defined as unexpected death due to a cardiac cause within a short timeframe, typically within 1 hour of the onset of symptoms, or within 24 hours of last being seen healthy if the death was unwitnessed. The most important cause of SCD is coronary atherosclerosis. Less commonly, it may be due to coronary vasospasm and other non-ischemic causes that include calcific aortic stenosis, endocarditis or myocarditis of various types, hypertrophic cardiomyopathy, mitral valve prolapses, endocarditis, and hereditary and acquired defects of the conduction system, or aortic aneurysm and dissection. The mechanism of SCD by myocardial ischemia is almost always due to development of fatal arrhythmias, chiefly ventricular asystole or fibrillation.

MORPHOLOGY At autopsy, such cases reveal most commonly *critical atherosclerotic narrowing* (more than 75% compromised lumen) in one or more of the three major coronary arterial trunks with superimposed thrombosis or plaque-hemorrhage. Healed and new myocardial infarcts are found in many cases.

Table 17.5 lists the important forms of coronary artery pathology in various types of IHD.

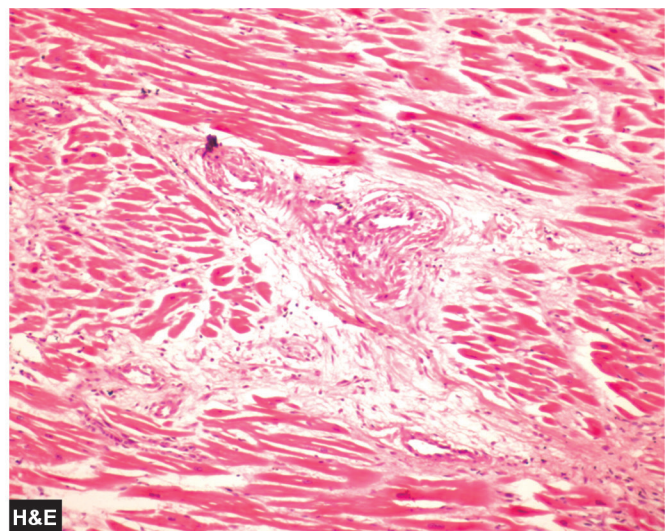
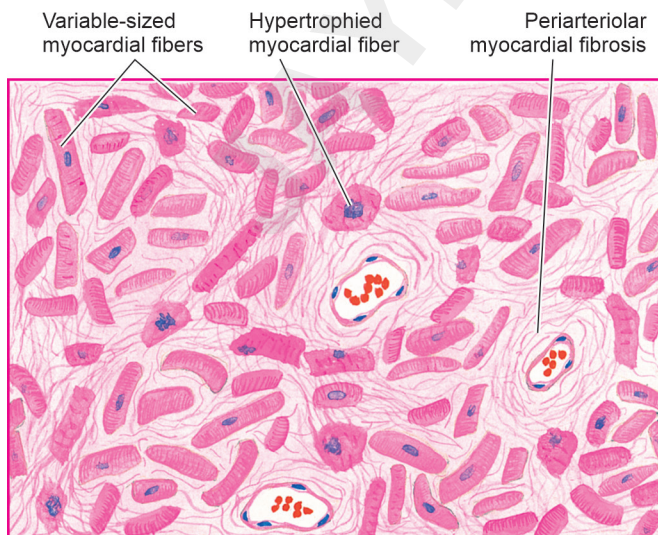
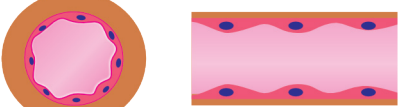


Figure 17.25 Chronic ischemic heart disease. There is patchy myocardial fibrosis, especially around small blood vessels in the interstitium. The intervening single cells and groups of myocardial cells show myocytolysis.

TABLE 17.5 Lesions in coronary artery in various forms of IHD.

	TYPES OF IHD	CORONARY LESION	CORONARY MORPHOLOGY*	CLINICAL EFFECTS
1.	<i>Stable angina</i>	➤ Critical coronary narrowing (3/4th)	 A, Normal	Chest pain occurs during exertion, subsides with rest or medication
2.	<i>Unstable (pre-infarction) angina</i>	➤ Chronic progressive coronary atherosclerosis ➤ Plaque rupture, hemorrhage, ulceration ➤ Mural thrombosis with thromboembolism	 B, Severe, fixed 3/4th narrowing	Longer duration of chest pain, often without exertion, and does not improve with rest or medications
3.	<i>Myocardial infarction</i>	➤ Plaque hemorrhage ➤ Fissuring and ulceration ➤ Complete mural thrombosis	 C, Thrombosis with hemorrhage	Crushing, squeezing, or burning sensation radiating to the left arm, shoulder, or jaw, shortness of breath. ECG changes
4.	<i>Sudden ischemic cardiac death</i>	➤ Severe multivessel disease ➤ Acute changes in plaque ➤ Thrombosis with thromboembolism	 D, Occlusive thrombosis	Unexplained death within 1 hour of onset of symptoms, or within 24-hours when the patient was last reported healthy

(IHD, ischemic heart disease; CIHD, chronic IHD).

*Figures on left are cross section and on right are longitudinal section of affected coronary artery.

SUMMARY Ischemic Heart Disease

Definition

- Ischemic heart disease (IHD) is a condition characterized by reduced blood flow to the heart muscle, causing an imbalance between the myocardial supply and demand for oxygenated blood.

Causes and Risk Factors

- **Atherosclerotic coronary artery disease (CAD)** The most common cause involving blockage of the LAD, RCA, and CXA arteries. Often accompanied by superimposed changes on the plaque.
- **Non-atherosclerotic causes** Emboli, coronary arteritis, myocarditis, coronary artery spasm, coronary dissection, cocaine abuse.
- **Risk factors** Hypertension, diabetes mellitus, smoking, high cholesterol, obesity, sedentary lifestyle, family history of heart disease.

Morphology

- **Gross features** Heart may be normal in size or hypertrophied. The affected left ventricular wall shows small gray-white foci of fibrosis against normal brown myocardium. Thinned out areas of healed scars of previous MI may be present. Coronary arteries show moderate to severe atherosclerosis.
- **Microscopic features** Scattered areas or diffuse myocardial fibrosis, especially around small blood vessels. Variation in fiber size and foci of myocytolysis. Atherosclerotic plaques in coronary arteries, sometimes with superimposed thrombosis.

Clinical Effects

- **Stable angina** Chest pain during exertion, subsiding with rest or medication.
- **Vasospastic (Prinzmetal variant angina)** Transient coronary spasm. Pain often at rest and during night, resolves.
- **Unstable angina** Chest pain for longer duration occurring unpredictably, often without exertion, and not improving with rest or medications.
- **Acute myocardial infarction (AMI)** Crushing, squeezing, or burning sensation radiating to left arm, shoulder, or jaw, shortness of breath. ECG changes and serum cardiac biomarkers help in diagnosis. Early thrombolytic therapy within 30 minutes may restore blood supply.
- **Chronic IHD** Focal or diffuse fibrosis in myocardium found in elderly patients with progressive IHD, leading to CHF or cardiac arrhythmias.

Complications

- **Immediate** Development of fatal arrhythmias, chiefly ventricular asystole or fibrillation, cardiogenic shock, cardiac rupture.
- **Delayed** CHF, mural thrombosis and thromboembolism, cardiac aneurysm, pericarditis, post-myocardial infarction syndrome.
- **Sudden cardiac death (SCD)** Unexpected death due to a cardiac cause within a short timeframe, typically within 1 hour of onset of symptoms or within 24 hours if witnessed.

RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE

Rheumatic fever (RF) is a systemic, post-streptococcal, nonsuppurative inflammatory disease, principally affecting the heart, joints, central nervous system, skin and subcutaneous tissues. The chronic stage of RF involves all the layers of the heart (pancarditis) causing major cardiac sequelae referred to as rheumatic heart disease (RHD). Despite its name suggesting an acute arthritis migrating from joint to joint, it is the heart rather than the joints which is first and major organ affected. Decades ago, William Boyd wrote the dictum for this disease—*rheumatism licks the joint but bites the whole heart*.

INCIDENCE

The disease appears most commonly in children between the age of 5 to 15 years when the streptococcal infection is most frequent and intense. It is the most common acquired heart disease in people under 25 years of age and accounts for about 2% of deaths from cardiovascular disease. Both the sexes are affected equally, though some investigators have noted a slight female preponderance.

The geographic distribution, incidence and severity of RF and RHD are generally related to the frequency and severity of streptococcal pharyngeal infection. The disease is seen more commonly in poor socioeconomic strata of society, and those living in damp and overcrowded places which promote interpersonal spread of the streptococcal infection. Its prevalence is high in low- and middle-income countries, particularly in sub-Saharan Africa, the Middle East, Central and South Asia, and the South Pacific. Its incidence has declined in the developed countries because of improved living conditions and early use of antibiotics in streptococcal infection, but is still more common amongst immigrants in high-income countries.

In India, RHD and RF continue to be a major public health problem; estimated average prevalence is 0.5 per 1,000 children in age group of 5–15 years.

ETIOPATHOGENESIS

After a prolonged controversy on etiology of RF, the role of preceding throat infection with group A β -hemolytic streptococci (GAS) is now well accepted. However, the mechanism of lesions in the heart, joints and other tissues is not by direct infection, but by induction of hypersensitivity or autoimmunity in a susceptible host. Thus, there are three groups of factors in the etiology and pathogenesis of RF and RHD: *environmental factors*, *host susceptibility* and *immunologic evidence*.

A. ENVIRONMENTAL FACTORS

There is sufficient clinical and epidemiological evidence to support the concept that RF occurs following infection of the throat and upper respiratory tract with β -hemolytic streptococci of Lancefield group A. Evidence in support is as under:

1. There is often a *history* of infection of the pharynx, upper respiratory tract with this microorganism about 2 to 3 weeks prior to the attack of RF. This period is usually the latent period required for sensitization to the bacteria. *Subsequent or ongoing attacks* of streptococcal infection are generally associated with recurrent episodes of acute RF.

2. A higher incidence of RF has been observed after outbreaks and *epidemics* of streptococcal infection of throat in children from schools or in young men from training camps.

3. Administration of *antibiotics* leads to lowering of the incidence as well as severity of RF and its recurrences.

4. The *geographic distribution* of the disease, as already pointed out, shows higher frequency and severity of the disease in the low- and middle-income countries of the world where the living conditions in underprivileged populations are substandard and medical facilities are insufficient. This is attributed to *socioeconomic factors* like poverty, poor nutrition, density of population, overcrowding in quarters for sleeping etc. These factors are associated with the spread of recurrent throat infections in children which remain untreated due to lack of proper medical attention and thus they have higher incidence of RF.

Despite all this evidence, only a small proportion of patients with streptococcal pharyngeal infection develop RF; usually this rate is less than 3% of all streptococcal infection. There is a suggestion that a *concomitant virus* enhances the effect of streptococci in individuals who develop RF.

B. HOST SUSCEPTIBILITY

Since all individuals with streptococcal infections do not develop RF, role of inherited characteristic for the disease has been reported, for example:

1. Clustering of disease in *families*.
2. Occurrence in *identical twins*.
3. Individuals with *HLA class II* alleles (particularly HLA-DR7 and HLA-DR4) have strong association with RF.
4. First-degree relatives of patients with RF and RHD have increased expression of a particular alloantigen, *D8-17*, on B cells, which may act as a marker for *inherited susceptibility* to the disease.
5. Association with host *polymorphisms* may contribute in developing RF and RHD. Examples include *TNF- α gene* (particularly the -308G/A) polymorphism leading to higher TNF- α activity, polymorphism in the *MBL2 gene* leading to defective infection clearance, and TLR polymorphism leading to altered response to group A-streptococcus.

C. IMMUNOLOGIC EVIDENCE

It has been observed that though streptococci are present during acute RF in the throat mucosa of patients, the clinical symptoms of RF in other organs appear after a delay of 2–3 weeks, and the organisms cannot be grown from the lesions in the target tissues. This indicates that the lesions in the heart possibly develop due to immune pathogenesis. Evidence in support is as under:

1. Patients with RF have *elevated titers* of antibodies to the antigens of β -hemolytic streptococci of group A such as anti-streptolysin O (ASO) and S, anti-streptokinase, anti-streptohyaluronidase and anti-DNAase B.
2. *Cell wall polysaccharide* of group A *Streptococcus* forms antibodies which are reactive against cardiac valves. This is supported by observation of persistently elevated corresponding autoantibodies in patients who have cardiac valvular involvement than those without cardiac valve involvement.
3. *Hyaluronate capsule* of group A *Streptococcus* is identical to human hyaluronate present in joint tissues and thus these tissues are the target of attack.
4. *Membrane antigens* of group A *Streptococcus* react with sarcolemma of smooth and cardiac muscle, dermal fibroblasts and neurons of caudate nucleus.

SUMMARY OF ORGANISM-HOST SUSCEPTIBILITY-IMMUNITY HYPOTHESIS

Combining the three types of evidence given above, pathogenesis of RF-RHD can be summed up as under (Fig. 17.26):

1. A susceptible host, on being encountered with group A *Streptococcus* infection, mounts an *autoimmune reaction* by formation of autoantibodies against bacteria.
2. These autoantibodies cause damage to human tissues due to *cross-reactivity* between epitopes in the components of bacteria and the host.
3. Streptococcal epitopes present on the bacterial cell wall, cell membrane and the *streptococcal M protein*, are immunologically identical to human molecules on myosin, keratin, actin, laminin, vimentin and N-acetylglucosamine.
4. *Molecular mimicry and cross-reactivity* between streptococcal M protein and the human molecules forms the basis of autoimmune damage to human target tissues in RHD, i.e. cardiac muscle, valves, joints, skin, neurons, etc.

MORPHOLOGY

RF is generally regarded as a disorder of type II hypersensitivity reaction of the connective tissues throughout the body. The *cardiac lesions* of RF in the form of pancarditis, particularly the valvular lesions, are its major manifestations. However, supportive connective tissues at other sites like the synovial membrane, periarticular tissue, skin and subcutaneous tissue, arterial wall, lungs, pleura and the CNS are all affected (*extracardiac lesions*).

A. Cardiac Lesions

The cardiac manifestations of RF are in the form of focal inflammatory involvement of the interstitial tissue of all the three layers of the heart, the so-called *pancarditis*. The pathognomonic feature of pancarditis in RF is the presence of distinctive *Aschoff nodules* or *Aschoff bodies*.

THE ASCHOFF NODULES OR BODIES

The Aschoff nodules or the Aschoff bodies are spheroidal or fusiform distinct tiny structures, 1–2 mm in size, occurring in the interstitium of the heart in RF and may be visible to naked eye. They are especially found in the vicinity of small blood vessels in the myocardium and endocardium and occasionally in the pericardium and the adventitia of the proximal part of the aorta. Lesions like the Aschoff nodules may be found in the extracardiac tissues.

Evolution of fully developed Aschoff bodies occurs through three stages, all of which may be found in the same heart at different stages of development. These are as follows:

1. Early (exudative or degenerative) stage The earliest sign of injury in the heart in RF is apparent by *about 4th week* of illness. Initially, there is edema of the connective tissue, and increase in the acid mucopolysaccharide in the ground substance. This results in fragmentation and degradation of collagen which takes the appearance and staining characteristics of fibrin; this change is referred to as *fibrinoid degeneration*.

2. Intermediate (proliferative or granulomatous) stage It is this stage of the Aschoff body which is pathognomonic of rheumatic conditions (Fig. 17.27). This stage is apparent in the 4th to 13th week of illness. The early stage of fibrinoid change is followed by proliferation of cells that includes infiltration by lymphocytes (mostly T cells), plasma cells, a few neutrophils and the characteristic *cardiac histiocytes* (*Anitschkow cells*) at the margin of the lesion. Cardiac histiocytes or Anitschkow cells are present in small number in normal heart, but their number is increased in the Aschoff bodies; therefore, they are not characteristic of RHD. Morphologically, these are large mononuclear cells having central round nuclei and contain moderate amounts of amphophilic cytoplasm. Their nuclei are vesicular and contain prominent central chromatin mass which in longitudinal section appears serrated or caterpillar-like, while in cross-section the chromatin mass appears as a small, rounded body in the center of the vesicular nucleus, just like an owl's eye. Some of these modified cardiac histiocytes become multinucleate cells containing 1 to 4 nuclei and are called *Aschoff cells* and these are pathognomonic of RHD.

3. Late (healing or fibrous) stage The stage of healing by fibrosis of the Aschoff nodule occurs in about *12 to 16 weeks* after the illness. The nodule becomes oval or fusiform in shape, about 200 µm wide and 600 µm long, frequently in perivascular location. The Anitschkow cells in the nodule become spindle-shaped with diminished cytoplasm and the nuclei stain solidly rather than showing vesicular character. With passage of time, the Aschoff body becomes less cellular, and the collagenous tissue is increased, resulting in a small fibrocollagenous scar having scanty cellularity.

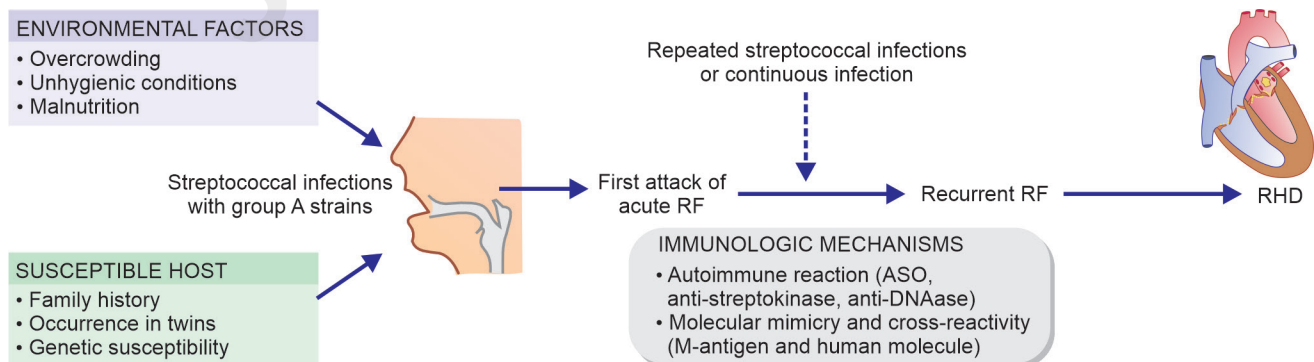


Figure 17.26 Pathogenesis of RHD, schematic evolution. (RF, rheumatic fever; RHD, rheumatic heart disease).

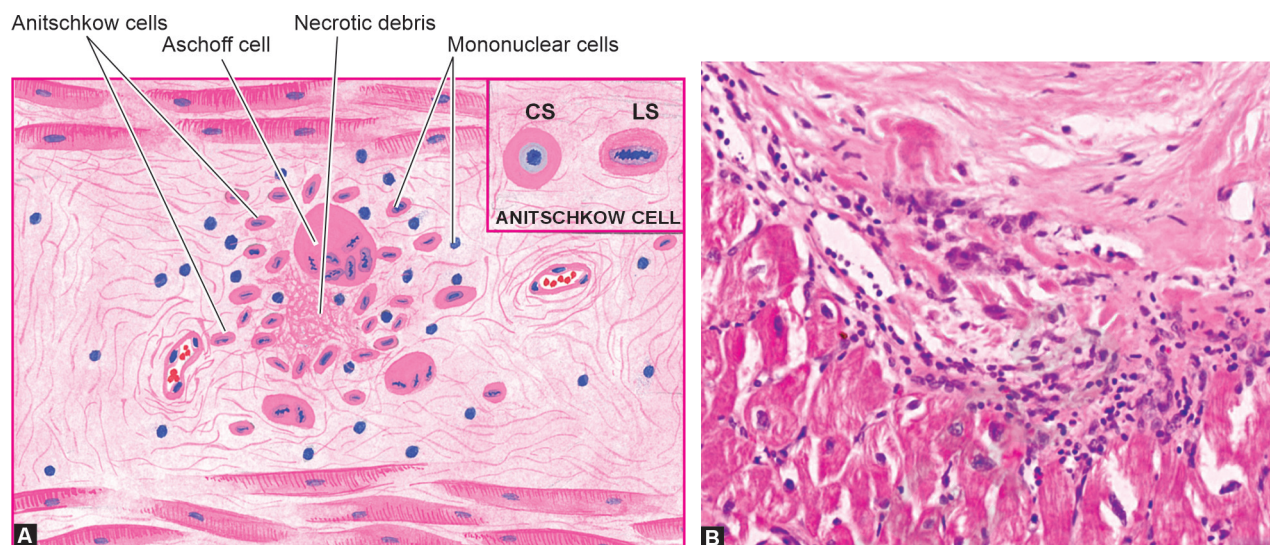


Figure 17.27 A, Aschoff body (granulomatous stage) in the myocardium. The lesion shows cardiac histiocytes (Anitschkow cells) and multinucleated fused cardiac histiocytes, called Aschoff cells. *Inset* shows Anitschkow cell in longitudinal section (LS) with caterpillar-like serrated nuclear chromatin, while cross-section (CS) shows owl-eye appearance of central chromatin mass and perinuclear halo. B, Microscopic image on right shows an Aschoff body in the myocardium, composed of Anitschkow cells and mononuclear cells. The Anitschkow cells show vesicular nuclei. (Image contributed by Dr Sudheer Arava, Professor of Pathology, AIIMS, New Delhi).

RHEUMATIC PANCARDITIS

Although all the three layers of the heart are affected in RF, the intensity of their involvement is variable.

1. RHEUMATIC ENDOCARDITIS Endocardial lesions of RF may involve the valvular and mural endocardium, causing *rheumatic valvulitis* and *mural endocarditis*, respectively. Rheumatic valvulitis is chiefly responsible for the major cardiac manifestations in chronic RHD.

RHEUMATIC VALVULITIS *Grossly*, the valves in **acute RF** show thickening and loss of translucency of the valve leaflets or cusps. This is followed by the formation of characteristic, small (1–3 mm in diameter), multiple, warty *vegetations* or *verrucae*, chiefly along the line of closure of the leaflets and cusps. These tiny vegetations are almost continuous so that the free margin of the cusps or leaflets appears as a rough and irregular ridge. The vegetations in RF appear gray-brown, translucent and are firmly attached so that they are not likely to get detached to form emboli, unlike the friable vegetations of infective endocarditis (page 482).

Though all the four heart valves are affected, their frequency and severity of involvement vary—mitral valve alone being the most common site, followed by the combined involvement of mitral and aortic valve (**Fig. 17.28**). The tricuspid and pulmonary valves usually show infrequent and slight involvement. The higher incidence of vegetations on the left side of the heart is possibly because of the greater mechanical stresses on the valves of the left heart, especially along the line of closure of the valve cusps (**Fig. 17.29, A**).

The **chronic stage of RHD** is characterized by permanent deformity of one or more valves, especially the mitral (in 98% cases alone or along with other valves) and aortic. The approximate frequency of deformity of major valves is as under:

- Mitral alone = 37% cases
- Mitral + aortic = 27% cases

- Mitral + aortic + tricuspid = 22% cases
- Mitral + tricuspid = 11% cases
- Aortic alone = 2%

The gross appearance of chronic healed mitral valve in RHD is characteristically ‘fish mouth’ or ‘buttonhole’ stenosis. Mitral stenosis and insufficiency are commonly combined in chronic RHD; calcific aortic stenosis may also be found (**Figs. 17.29, B, C**).

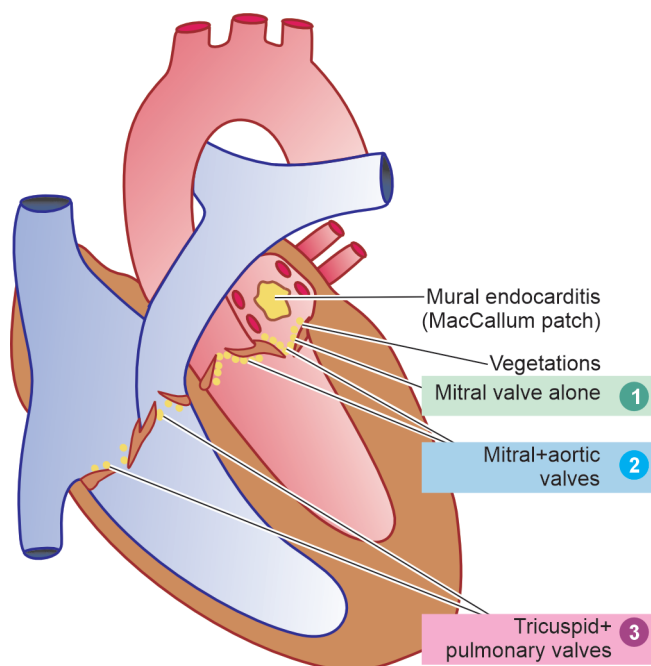


Figure 17.28 Schematic representation of the anatomic regions of involvement and location of vegetations in rheumatic endocarditis (both valvular and mural). Serial numbers 1, 2 and 3 are denoted for the frequency of valvular involvement.

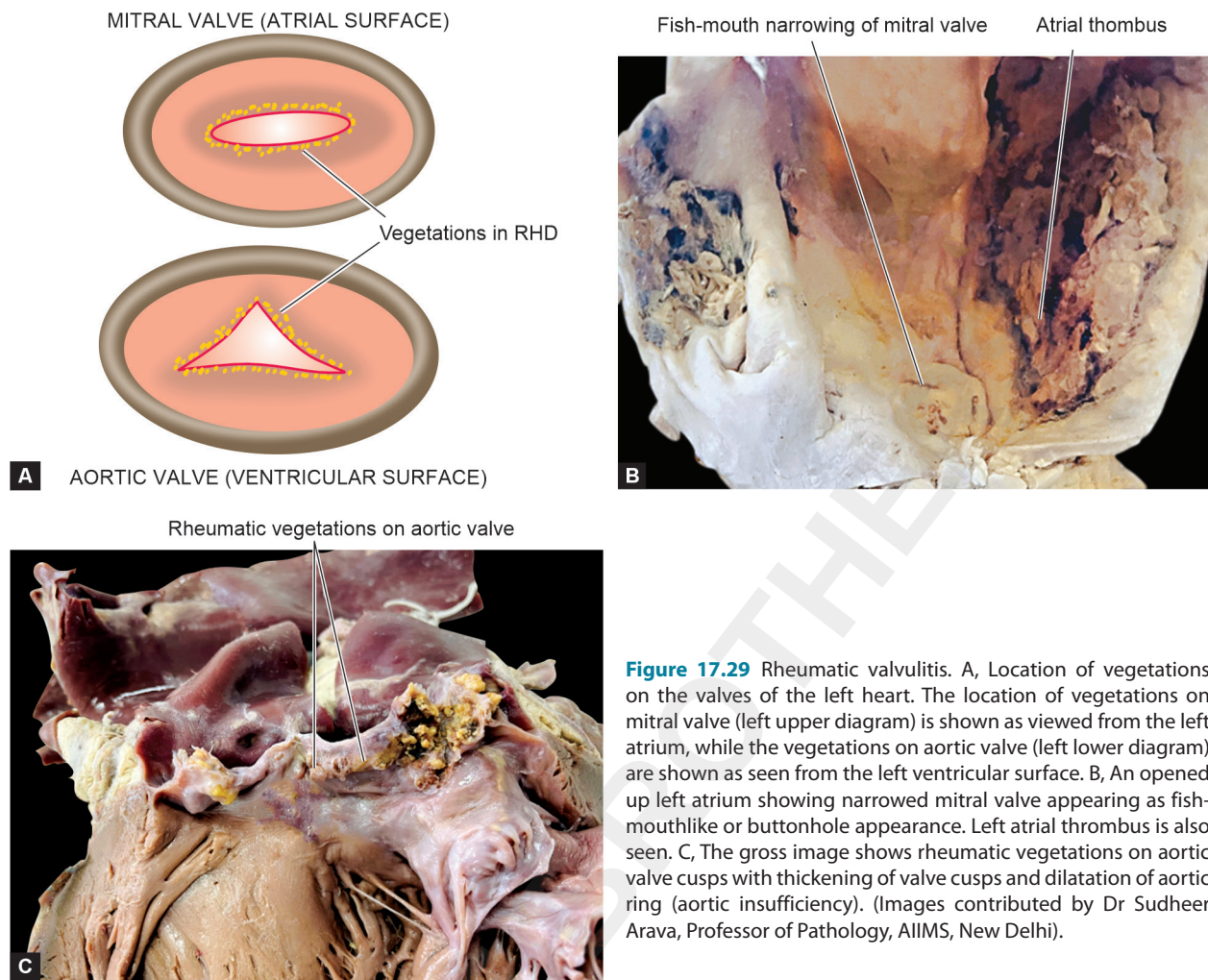


Figure 17.29 Rheumatic valvulitis. A, Location of vegetations on the valves of the left heart. The location of vegetations on mitral valve (left upper diagram) is shown as viewed from the left atrium, while the vegetations on aortic valve (left lower diagram) are shown as seen from the left ventricular surface. B, An opened up left atrium showing narrowed mitral valve appearing as fish-mouthlike or buttonhole appearance. Left atrial thrombus is also seen. C, The gross image shows rheumatic vegetations on aortic valve cusps with thickening of valve cusps and dilatation of aortic ring (aortic insufficiency). (Images contributed by Dr Sudheer Arava, Professor of Pathology, AIIMS, New Delhi).

Microscopically, the inflammatory changes begin in the region of the valve rings (where the leaflets are attached to the fibrous annulus) and then extend throughout the entire leaflet, whereas vegetations are usually located on the free margin of the leaflets and cusps:

- i) In the **early (acute) stage**, the histological changes are edema of the valve leaflet, presence of increased number of capillaries and infiltration with lymphocytes, plasma cells, histiocytes with many Anitschkow cells and a few polymorphs. Occasionally, Aschoff bodies with central foci of fibrinoid necrosis and surrounded by palisade of cardiac histiocytes are seen, but more often the cellular infiltration is diffuse in acute stage of RF. Vegetations present at the free margins of cusps appear as eosinophilic, tiny structures mainly consisting of fibrin with superimposed platelet-thrombi and do not contain bacteria (**Fig. 17.30, A**).
- ii) In the **healed (chronic) stage**, the vegetations have undergone organization. The valves show diffuse thickening because of fibrosis with hyalinization, and often calcification. Vascularization of the valve cusps may still be evident in the form of thick-walled blood vessels with narrowed lumina (**Fig. 17.30, B**). Typical Aschoff bodies are rarely seen in the valves at this stage.

RHEUMATIC MURAL ENDOCARDITIS Mural endocardium may also show features of rheumatic carditis though the changes are less conspicuous as compared to valvular changes. One of the most characteristic changes is the *MacCallum patch* or *MacCallum triangle*, identified as thickened, roughened, and wrinkled triangular area of the endocardium, particularly in the posterior wall of left atrium. This is because of recurrent injury caused by regurgitant blood stream in case of rheumatic mitral valvulitis.

Grossly MacCallum patch appears as a map-like area of thickened, roughened and wrinkled part of the endocardium (see **Fig. 17.28**).

Microscopically, MacCallum patch shows histological features of inflammation, including lymphocytic infiltration and the presence of Aschoff bodies, similar to that seen in rheumatic valvulitis.

2. RHEUMATIC MYOCARDITIS **Grossly**, in the *early (acute) stage*, the myocardium, especially of the left ventricle, is soft and flabby. In the *intermediate stage*, the interstitial tissue of the myocardium shows small foci of necrosis. Later, tiny pale foci of the Aschoff bodies may be visible throughout the myocardium.

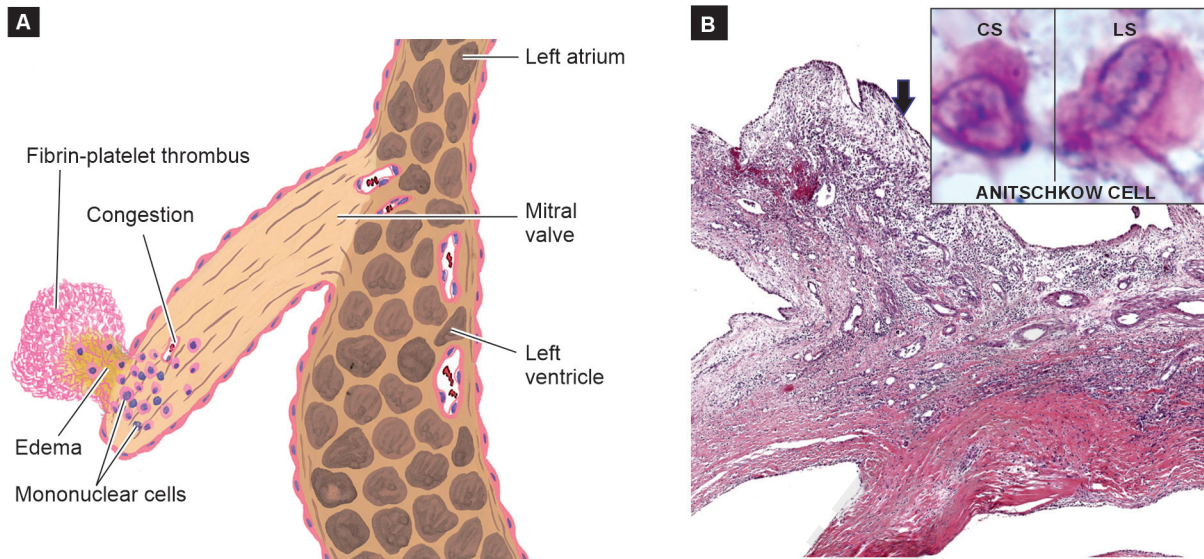


Figure 17.30 Rheumatic heart disease. A, Diagrammatic appearance of rheumatic valvulitis and one vegetation on the cusp of mitral valve in the sagittal section. B, Rheumatic valvular endocarditis showing valve deformed by an elevated vegetation composed of granulation tissue (arrow). Inset shows an Anitschkow cell in cross section (CS) and in longitudinal section (LS). (Microimage reproduced with permission from *Atlas of Histopathology* by Ivan Damjanov 2012, Jaypee Brothers Medical Publishers Pvt Ltd, New Delhi).

Microscopically, the most characteristic feature of rheumatic myocarditis is the presence of distinctive Aschoff bodies. These diagnostic nodules are scattered throughout the interstitial tissue of the myocardium and are most frequent in the interventricular septum, left ventricle and left atrium. Derangements of the conduction system may, thus, be present. The Aschoff bodies are best identified in the intermediate stage when they appear as granulomas with central fibrinoid necrosis and are surrounded by palisade of Anitschkow cells and multinucleate Aschoff cells. There is infiltration by lymphocytes, plasma cells and some neutrophils (see Fig. 17.27). In the late stage, the Aschoff bodies are gradually replaced by small fibrous scars in the vicinity of blood vessels and the inflammatory infiltrate subsides. The presence of active Aschoff bodies within healed fibrous lesions is indicative of ongoing rheumatic activity (Fig. 17.31).

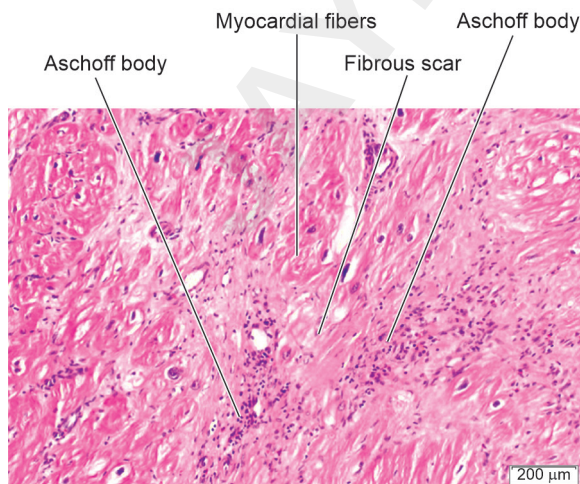


Figure 17.31 Rheumatic myocarditis. It shows an old rheumatic lesion in the myocardium having fibrous scar, along with a few active Aschoff bodies, indicative of ongoing rheumatic activity (The image contributed by Dr Sudheer Arava, Professor of Pathology, AIIMS, New Delhi).

3. RHEUMATIC PERICARDITIS Inflammatory involvement of the pericardium commonly accompanies RHD.

Grossly, the usual finding is fibrinous pericarditis in which there is loss of normal shiny pericardial surface due to deposition of fibrin on its surface and accumulation of slight amount of fibrinous exudate in the pericardial sac. If the parietal pericardium is pulled off from the visceral pericardium, the two separated surfaces are shaggy due to thick fibrin covering them. This appearance is often likened to 'bread and butter appearance', i.e. resembling the buttered surfaces of two slices in a sandwich when they are gently pulled apart. If fibrinous pericarditis fails to resolve and, instead, undergoes organization, the two layers of the pericardium form permanent fibrous adhesions resulting in chronic adhesive pericarditis.

Microscopically, fibrin is identified on the surfaces. The subserosal connective tissue is infiltrated by lymphocytes, plasma cells, histiocytes and a few neutrophils (Fig. 17.32). Characteristic Aschoff bodies may be seen which later undergo organization and fibrosis.

B. Extracardiac Lesions

Patients of the syndrome of acute rheumatism develop lesions in connective tissue elsewhere in the body, chiefly the joints, subcutaneous tissue, arteries, brain and lungs.

1. POLYARTHRITIS Acute and painful inflammation of the synovial membranes of some of the joints, especially the larger joints of the limbs, is seen in about 90% cases of RF in adults and less often in children. As pain and swelling subside in one joint, others tend to get involved, producing the characteristic 'migratory polyarthritis' involving two or more joints at a time.

2. SUBCUTANEOUS NODULES The subcutaneous nodules of RF occur more often in children than in adults. These nodules are small (0.5–2 cm in diameter), spherical or ovoid and painless. Characteristic locations of these nodules are tendons

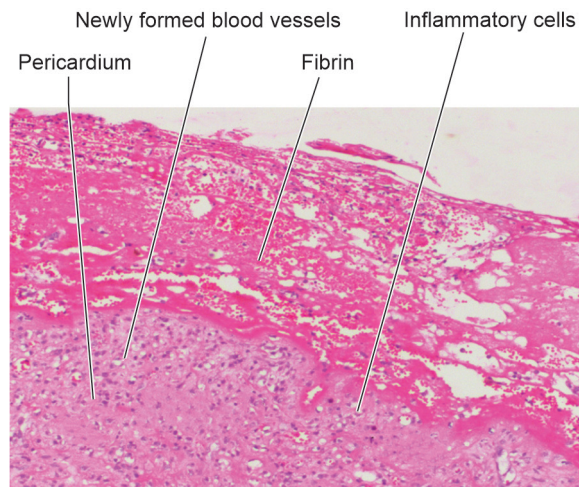


Figure 17.32 Rheumatic pericarditis. The surface of pericardium shows fibrin and inflammatory cells, while the underlying tissue shows chronic inflammatory cells and newly-formed vessels. (The image contributed by Dr Sudheer Arava, Professor of Pathology, AIIMS, New Delhi).

and ligaments of the extensor surfaces of the wrists, elbows, ankles and knees.

Histologically, the subcutaneous nodules of RF are representative of giant Aschoff bodies seen in the heart. They consist of three distinct zones: a central area with fibrinoid changes, surrounded by a zone of histiocytes and fibroblasts forming a palisade arrangement, and the outermost zone of connective tissue which is infiltrated by non-specific chronic inflammatory cells and proliferating blood vessels.

It may be mentioned here that histologically similar but clinically different subcutaneous lesions appear in rheumatoid arthritis; they are larger, painful and tender and persist for months to years (page 937).

3. ERYTHEMA MARGINATUM This non-pruritic erythematous rash is characteristic of RF. The lesions occur mainly on the trunk and proximal parts of the extremities. The erythematous area develops central clearing and has slightly elevated red margins. The erythema is transient and migratory.

4. RHEUMATIC ARTERITIS Other than the coronary arteries and aorta, rheumatic arteritis can also be seen in renal, mesenteric and cerebral arteries. In the coronary arteries, rheumatic arteritis is noted in small intramyocardial branches.

5. CHOREA MINOR Chorea minor or Sydenham chorea or Saint Vitus dance is a delayed manifestation of RF because of involvement of the basal ganglia in central nervous system. The condition is characterized by involuntary, jerky movements (chorea), muscle weakness, and emotional instability. This condition occurs more often in younger age, particularly in girls.

6. RHEUMATIC PNEUMONITIS AND PLEURITIS Involvement of the lungs and pleura occurs rarely in RF. Pleuritis is often accompanied with serofibrinous pleural effusion, but definite Aschoff bodies are not present. In rheumatic pneumonitis, the lungs are large, firm and rubbery.

CLINICAL FEATURES, DIAGNOSIS AND PROGNOSIS

The first episode of acute RF generally appears 2 to 3 weeks after streptococcal pharyngitis, most often in children in the age-range of 5 to 15 years. With subsequent streptococcal pharyngitis, there is reactivation of the disease with appearance of similar clinical manifestations with each recurrent episode. The disease generally presents with migratory polyarthritides and fever. There is no single specific clinical feature or laboratory test for diagnosis of RF. Based on *revised Jones criteria* (first described by Dr TD Jones in 1944, and twice revised by the American Heart Association in 1992 and 2015) that takes into account low, medium and high-risk population, following major and minor criteria and some supportive evidence of preceding infection are included for diagnosis:

A. Major criteria

1. Carditis (50–75% cases): Clinical or subclinical identified on doppler echocardiography
2. Arthritis (60–75% cases): Polyarthritides or monoarthritides
3. Chorea (Sydenham chorea) (2–30% cases)
4. Erythema marginatum (<5%)
5. Subcutaneous nodules (<5%)

B. Minor criteria

1. Fever ($\geq 38.5^{\circ}\text{C}$ or 100.4°F)
2. Polyarthralgia, without other signs of inflammation
3. Previous history of RF
4. Laboratory indicators of acute phase: Elevated ESR (>60 mm 1st hour) or raised C-reactive protein (>3 mg/dL)
5. Prolonged PR interval in ECG

C. Supportive evidence of group A streptococcal infection in preceding 45 days

1. Positive throat culture for group A streptococci
2. Raised titers of streptococcal antibodies (antistreptolysin O and S, anti-streptokinase, anti-streptohyaluronidase and anti-DNAse B).

Clinical **diagnosis of RF and RHD** is made in a case with antecedent laboratory evidence of streptococcal throat infection in the presence of *any two of the major criteria, or occurrence of one major plus two minor criteria*.

If the heart is spared in a case of acute RF, the patient may have complete recovery without any sequelae. However, once the heart is involved, it is often associated with reactivation and recurrences of the disease. Myocarditis is the most life-threatening due to involvement of the conduction system of the heart and results in serious arrhythmia. The **long-term sequelae** or **stigmata** are the chronic valvular deformities, especially the mitral stenosis or regurgitation, as already explained. Initially, a state of compensation occurs, while later decompensation of the heart leads to full-blown cardiac failure. However, surgical replacement of the damaged valves can alter the clinical course of the disease.

The major **causes of death** in RHD are cardiac failure, bacterial endocarditis and embolism:

1. **Cardiac failure** is the most common cause of death from RHD. In young patients, cardiac failure occurs due to the chronic

valvular deformities, while in older patients coronary artery disease may be superimposed on the old RHD.

2. *Bacterial endocarditis* of both acute and subacute type may supervene due to inadequate use of antibiotics.
3. *Embolism* in RHD originates most commonly from mural thrombi in the left atrium and its appendages, associated with mitral stenosis. The organs most frequently affected are the brain, kidneys, spleen and lungs.
4. *Sudden death* may occur in RHD because of ball thrombus in the left atrium or due to acute coronary insufficiency in association with aortic stenosis.

SUMMARY Rheumatic Fever and Rheumatic Heart Disease

Causes

- Post-streptococcal, non-suppurative inflammatory disease
- Triggered by Group A β -hemolytic streptococcal throat infection

Pathophysiology

- Autoimmune reaction in a susceptible host
- Formation of autoantibodies causing tissue damage
- Molecular mimicry and cross-reactivity between streptococcal M protein and human tissues

Cardiac Lesions

- *Aschoff bodies* Significant morphologic feature; granulomas with central fibrinoid necrosis surrounded by Anitschkow cells
- *Pancarditis* All three layers of the heart involved:
 - ◆ Endocarditis—Rheumatic valvulitis leading to thickening, vegetations, and deformity of valves, especially mitral and aortic; rheumatic mural endocarditis
 - ◆ Myocarditis—Interstitial inflammatory lesions, particularly in left ventricle and the septum
 - ◆ Pericarditis—Fibrinous pericarditis with ‘bread and butter’ appearance

Extracardiac Lesions

- *Polyarthritides* Migratory inflammation of large joints
- *Subcutaneous nodules* Painless, small nodules on extensor surfaces
- *Erythema marginatum* Non-pruritic rash with red margins
- *Chorea minor* Involuntary movements and muscle weakness
- *Pleuritis* Serofibrinous effusion in pleural cavity

Diagnostic Criteria

- Antecedent laboratory evidence of streptococcal throat infection in the presence of any two of the major criteria, or occurrence of one major plus two minor criteria as per modified Jones criteria (2015)

Complications

- Chronic valvular deformities (mitral stenosis or regurgitation)
- Heart failure
- Bacterial endocarditis
- Embolism (originating from mural thrombi)
- Sudden death due to ball thrombus or acute coronary insufficiency

NON-RHEUMATIC ENDOCARDITIS

Inflammatory involvement of the endocardial layer of the heart is called endocarditis. In common usage, if not specified,

endocarditis would mean inflammation of the valvular endocardium; the term mural endocarditis is used for similar change on the inner lining of the lumina of cardiac chambers. Endocarditis can be broadly grouped into *non-infective* and *infective* types (Table 17.6). Most types of endocarditis are characterized by the presence of ‘vegetations’ or ‘verrucae’ which have distinct features.

LIBMAN-SACKS ENDOCARDITIS

Libman and Sacks, two American physicians, described a form of non-bacterial endocarditis in 1924 that is characterized by sterile endocardial vegetations which are distinct from the vegetations of RHD and bacterial endocarditis; hence also called atypical verrucous or non-bacterial verrucous endocarditis.

ETIOPATHOGENESIS Characteristic lesions of Libman-Sacks endocarditis are seen in collagen vascular diseases (50% cases of systemic lupus erythematosus or SLE, some cases of systemic sclerosis, and anti-phospholipid lupus antibody or APLA syndrome).

MORPHOLOGY *Grossly*, characteristic vegetations occur most frequently on the mitral and tricuspid valves. The vegetations of atypical verrucous endocarditis are small (1 to 4 mm in diameter), granular, multiple and tend to occur on both surfaces of affected valves, in the valve pockets and on the adjoining ventricular and atrial endocardium. The vegetations are sterile unless they are superimposed by bacterial endocarditis. Unlike vegetations of RHD, the healed vegetations of Libman-Sacks endocarditis do not produce any significant valvular deformity. Frequently, fibrinous or serofibrinous pericarditis with pericardial effusion is associated.

Microscopically, the verrucae of Libman-Sacks endocarditis are composed of fibrinoid material with superimposed fibrin and platelet thrombi. The endocardium underlying the verrucae shows characteristic histological changes which include fibrinoid necrosis, proliferation of capillaries and infiltration by histiocytes, plasma cells, lymphocytes, neutrophils and the pathognomonic *hematoxylin bodies* of Gross which are counterparts of LE cells of the blood.

NON-BACTERIAL THROMBOTIC ENDOCARDITIS

Non-bacterial thrombotic endocarditis (NBTE) is an involvement of the heart valves by sterile thrombotic vegetations. Since NBTE is seen in association with chronic debilitating and wasting diseases, it is also called ‘cachectic,’ ‘marantic’ and ‘terminal’ endocarditis. NBTE vegetations are found at autopsy in 0.5 to 5% of cases.

TABLE 17.6 Classification of endocarditis.

A. NON-INFECTIVE	
	1. Rheumatic endocarditis (page 476)
	2. Libman-Sacks (or atypical verrucous) endocarditis
	3. Non-bacterial thrombotic endocarditis
B. INFECTIVE	
	1. Bacterial endocarditis
	2. Other infective types (tuberculous, syphilitic, fungal, viral, rickettsial)

ETIOPATHOGENESIS The exact pathogenesis of lesions in NBTE is not clear. A state of hypercoagulability from different causes predisposes to NBTE, e.g. advanced cancer (in 50% case of NBTE) especially mucinous adenocarcinomas. Besides, NBTE is also seen in association with chronic wasting and debilitating diseases, e.g. chronic tuberculosis, renal failure and chronic sepsis.

MORPHOLOGY *Grossly*, the verrucae of NBTE are located on cardiac valves, chiefly mitral, and less often on aortic and tricuspid valve. These verrucae are usually small (1 to 5 mm in diameter), single or multiple, brownish and occur along the line of closure of the leaflets, but are more friable than the vegetations of RHD. Organized and healed vegetations appear as fibrous nodules. Normal age-related appearance of tag-like appendage at the margin of the valve cusps known as 'Lambl excrescences' is an example of such healed lesions. Lambl excrescences are common on aortic or mitral valves.

Microscopically, the vegetations in NBTE are composed of fibrin along with entangled RBCs, WBCs and platelets. Vegetations in NBTE are sterile, bland and do not cause tissue destruction. The underlying valve shows swollen collagen, fibrinoid change and capillary proliferation, but devoid of any inflammatory infiltrate.

As the vegetations in NBTE are friable, embolic phenomenon is seen in many cases resulting in infarcts in the brain, lungs, spleen and kidneys. The bland vegetations of NBTE may become infected and produce infective endocarditis.

INFECTIVE (BACTERIAL) ENDOCARDITIS

DEFINITION Infective or bacterial endocarditis (IE or BE) is a serious infection of the valvular and mural endocardium caused by different forms of microorganisms and is characterized by typical infected and friable vegetations. A few specific forms of IE are named by the microbial etiologic agent causing them, e.g. tubercle bacilli, fungi, etc. Depending upon the severity of infection, BE is subdivided into two clinical forms:

1. Acute bacterial endocarditis (ABE) is a fulminant and destructive acute infection of the endocardium by highly virulent bacteria in a previously normal heart and almost invariably runs a rapidly fatal course within 2–6 weeks.

2. Subacute bacterial endocarditis (SABE) or endocarditis lenta (*lenta*=slow) is caused by less virulent bacteria in a previously diseased heart and has a gradual downhill course in a period of 6 weeks to a few months and sometimes years.

Although classification of bacterial endocarditis into acute and subacute forms has been largely discarded because the clinical course is altered by antibiotic treatment, still there are a few important distinguishing features (Table 17.7). However, features of the vegetations in the two forms of BE are difficult to distinguish.

INCIDENCE Introduction of antibiotic drugs has helped greatly in lowering the incidence of BE as compared with its incidence in the pre-antibiotic era. Though BE may occur at any age, most cases of ABE as well as SABE occur over 50 years of age. Males are affected more often than females.

TABLE 17.7 Distinguishing features of acute and subacute bacterial endocarditis.

	FEATURE	ACUTE	SUBACUTE
1.	Duration	<6 weeks	>6 weeks
2.	Most common organisms	<i>Staph. aureus</i> , β -streptococci	<i>Streptococcus viridians</i>
3.	Virulence of organisms	Highly virulent	Less virulent
4.	Previous condition of valves	Usually previously normal	Usually previously damaged
5.	Lesion on valves	Invasive, destructive, suppurative	Usually not invasive or suppurative
6.	Clinical features	Features of acute systemic infection	Splenomegaly, clubbing of fingers, petechiae

ETIOLOGY All cases of BE are caused by *infection with microorganisms* in patients having certain *predisposing factors*.

A. Infective agents About 90% cases of BE are caused by streptococci and staphylococci.

- In ABE, the most common causative organisms are virulent strains of staphylococci, chiefly *Staphylococcus aureus*. Others are pneumococci, gonococci, β -streptococci, and enterococci (*S. faecalis*).

- In SABE, the commonest causative organisms are the streptococci with low virulence, predominantly *Streptococcus viridans*, which forms part of normal flora of the mouth and pharynx. Other less common etiologic agents include other strains of streptococci and staphylococci (e.g. *Streptococcus bovis* which is the normal inhabitant of gastrointestinal tract, *Streptococcus pneumoniae*, and *Staphylococcus epidermidis* which is a commensal of the skin), gram-negative enteric bacilli (e.g. *E. coli*, *Klebsiella*, *Pseudomonas* and *Salmonella*), pneumococci, gonococci and *Hemophilus influenzae*.

B. Predisposing factors There are three main types of factors which predispose to the development of both forms of BE:

- Conditions initiating transient bacteremia, septicemia and pyemia

- Underlying heart disease
- Impaired host defenses

1. Bacteremia, septicemia and pyemia Bacteria gain entry to the blood stream causing transient and clinically silent bacteremia in a variety of day-to-day procedures as well as from other sources of infection. For example:

- Periodontal infections such as trauma from vigorous brushing of teeth, hard chewing, tooth extraction and other dental procedures.
- Infections of the genitourinary tract such as in catheterization, cystoscopy, obstetrical procedures including normal delivery and abortions.
- Infections of gastrointestinal and biliary tract.
- Surgery of the bowel, biliary tract and genitourinary tracts.
- Skin infections such as boils, carbuncles and abscesses.
- Upper and lower respiratory tract infections like bacterial pneumonias.
- Intravenous drug abuse.
- Cardiac catheterization and cardiac surgery for implantation of prosthetic valves.

2. **Underlying heart disease** SABE occurs much more frequently in previously diseased heart valves, whereas the ABE is common in previously normal heart. Some of the commonly associated underlying heart diseases are as follows:

- i) Chronic rheumatic valvular disease in about 50% cases.
 - ii) Congenital heart diseases in about 20% cases. These include VSD, subaortic stenosis, pulmonary stenosis, bicuspid aortic valve, coarctation of the aorta, and PDA.
 - iii) Other causes are syphilitic aortic valve disease, atherosclerotic valvular disease, floppy mitral valve, and prosthetic heart valves.
3. **Impaired host defenses** All conditions in which there is impairment of specific immunity, deficiency of complement and defective phagocytic function, predispose to BE. For example:
- i) Impaired specific immunity in lymphomas
 - ii) Leukemias
 - iii) Cytotoxic therapy for various forms of cancer and transplant patients
 - iv) Deficient functions of neutrophils and macrophage

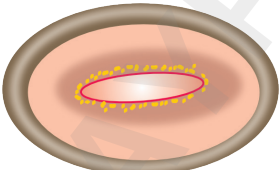
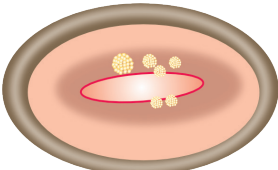
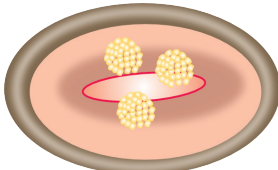
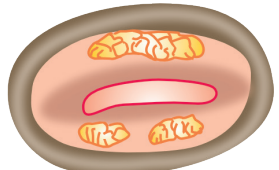
PATHOGENESIS Bacteria causing BE, on entering the blood stream from any of the above-mentioned routes, are implanted on the cardiac valves or mural endocardium because they have surface adhesion molecules, which mediate their adherence to injured endocardium. The circulating bacteria are lodged much more frequently on *previously damaged valves* than on healthy valves, e.g. RHD, congenital heart diseases and prosthetic valves.

MORPHOLOGY The characteristic pathologic feature in both ABE and SABE is the presence of typical vegetations or verrucae on the valve cusps or leaflets, and less often on mural endocardium, which are quite distinct for other types. A summary of the distinguishing features of the principal types of vegetations is presented in **Table 17.8**.

Grossly, the lesions are found commonly on the valves of the left heart, most frequently on the mitral, followed in descending frequency, by the aortic, simultaneous involvement of both mitral and aortic valves, and quite rarely on the valves of the right heart. The vegetations in SABE are more often seen on previously diseased valves, whereas the vegetations of ABE are often found on previously normal valves. Like in RHD, the vegetations are often located on the atrial surface of atrioventricular valves and ventricular surface of the semilunar valves. They begin from the contact areas of the valve and may extend along the surface of the valves and on to the adjacent endocardium (**Fig. 17.33**).

The *vegetations* of BE vary in size from a few millimeters to several centimeters, gray-tawny to greenish, irregular, single or multiple, and typically *friable*. They may appear flat, filiform, fungating or polypoid. The vegetations in ABE tend to be bulkier and globular than those of SABE and are located more often on previously normal valves, may cause ulceration or perforation of the underlying valve leaflet, or may produce myocardial abscesses.

TABLE 17.8 Distinguishing features of vegetations in major forms of endocarditis.

FEATURE	RHEUMATIC	LIBMAN-SACKS	NON-BACTERIAL THROMBOTIC	BACTERIAL (INFECTIVE)
1. <i>Valves commonly affected</i>	Mitral alone; mitral and aortic combined	Mitral, tricuspid	Mainly mitral; less often aortic and tricuspid	Mitral; aortic; combined mitral and aortic
2. <i>Location on valve cusps or leaflets</i>	Occur along the line of closure, atrial surface of atrioventricular valves and ventricular surface of semilunar valves	Occur on both surfaces of valve leaflets or cusps, in the valve pockets	Occur along the line of closure	SABE more often on diseased valves; ABE on previously normal valves; location same as in RHD
3. <i>Gross appearance</i>	 Small, multiple, warty, gray-brown, translucent, firmly attached, generally produce permanent valvular deformity	 Medium-sized, multiple, generally do not produce significant valvular deformity	 Small but larger than those of rheumatic, single or multiple, brownish, firm, but more friable than those of rheumatic	 Often large, gray-tawny to greenish, irregular, single or multiple, typically friable
4. <i>Microscopy</i>	i. Composed of fibrin with superimposed platelet thrombi and no bacteria. ii. Adjacent and underlying endocardium shows edema, proliferation of capillaries, mononuclear inflammatory infiltrate and occasional Aschoff bodies.	i. Composed of fibrinoid material with superimposed fibrin and platelet thrombi and no bacteria. ii. The underlying endocardium shows fibrinoid necrosis, proliferation of capillaries and acute and chronic inflammatory infiltrate including the hematoxylin bodies of Gross.	i. Composed of degenerated valvular tissue, fibrin platelets thrombi and no bacteria. ii. The underlying valve shows swelling of collagen, fibrinoid change, proliferation of capillaries but no significant inflammatory infiltrate.	i. Composed of outer eosinophilic zone of fibrin and platelets, covering colonies of bacteria and deeper zone of nonspecific acute and chronic inflammatory cells. ii. The underlying endocardium may show abscesses in ABE and inflammatory granulation tissue in the SABE.

(ABE, acute bacterial endocarditis; SABE, subacute bacterial endocarditis; RHD, rheumatic heart disease).

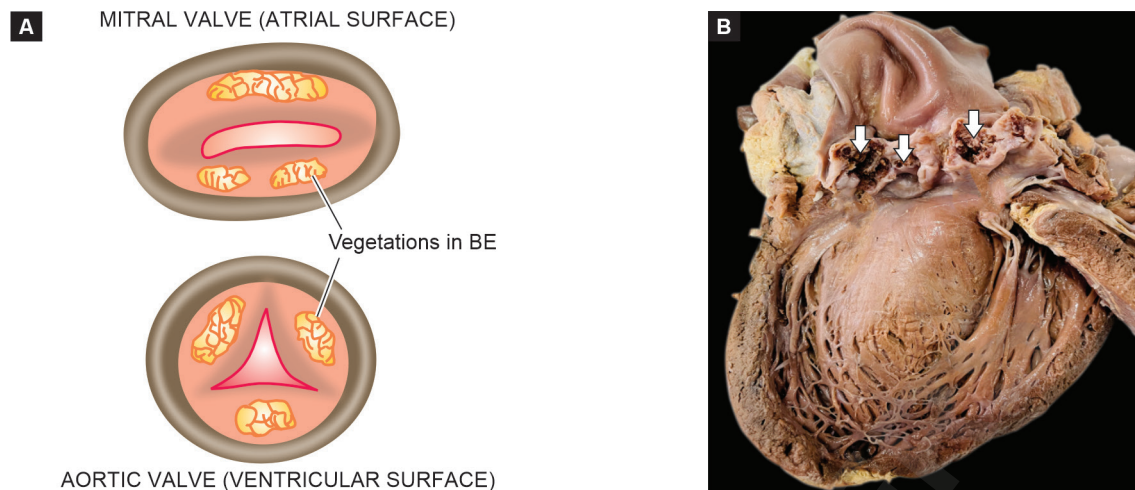


Figure 17.33 Infective endocarditis. A, Schematic location of vegetations on the valves of the left heart. The vegetations are shown on the mitral valve (left upper diagram) as viewed from the left atrium, while those on the aortic valve (left lower diagram) are shown as seen from the left ventricle. B, Infective endocarditis. Left side of the heart is opened up and shows large, irregular, gray-white friable vegetations on the atrial (superior) surface of the mitral valve (arrow) which is ruptured. (The image contributed by Dr Sudheer Arava, Professor of Pathology, AIIMS, New Delhi).

Microscopically, the vegetations of BE consist of three zones (**Fig. 17.34**):

- The *outer layer or cap* consists of eosinophilic material composed of fibrin and platelets.
- Underneath this layer is the *basophilic zone* containing colonies of bacteria. However, bacterial components of the vegetations may be lacking in treated cases.
- The *deeper zone* consists of non-specific inflammatory reaction in the cusp itself, and in the case of SABE there may be evidence of repair.

In the acute fulminant form of the disease, the inflammatory cell infiltrate chiefly consists of neutrophils and is accompanied by tissue necrosis and abscesses in the valve rings and in the myocardium. In the subacute form, there is healing by granulation tissue, mononuclear

inflammatory cell infiltration and fibroblastic proliferation. Histological evidence of pre-existing valvular diseases such as RHD may be present in SABE.

COMPLICATIONS In the early stage, the lesions are confined to the heart, while subsequent progression of the disease leads to involvement of extracardiac organs. In general, severe complications develop earlier in ABE than in SABE. Complications and sequelae of BE are divided into cardiac and extracardiac (**Fig. 17.35**):

I. Cardiac complications These include the following:

- Valvular stenosis or insufficiency
- Perforation, rupture, and aneurysm of valve leaflets
- Abscesses in the valve ring
- Myocardial abscesses

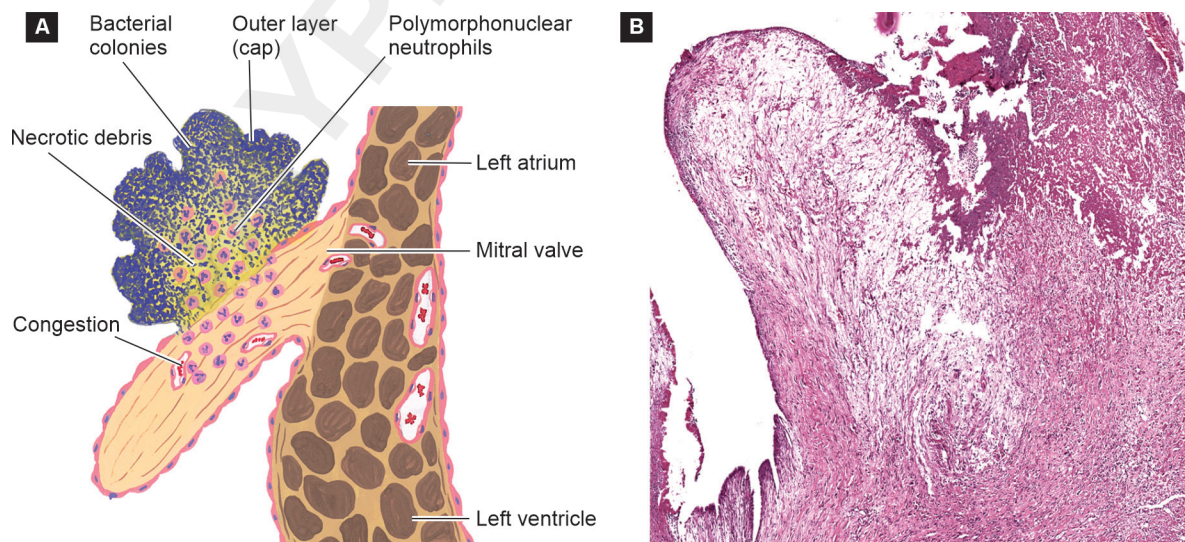


Figure 17.34 Infective endocarditis. A, Diagrammatic appearance of a vegetation of IE on the surface of mitral valve in sagittal section. B, Histology of infective endocarditis vegetation on mitral valve. The vegetation is composed of fibrin, acute neutrophilic exudate and a blue layer of bacterial colonies. The *inbox* shows Gram-stained valvular BE vegetation, highlighting the Gram-positive organisms. (Microimage reproduced with permission from *Atlas of Histopathology* by Ivan Damjanov 2012, Jaypee Brothers Medical Publishers Pvt Ltd, New Delhi).

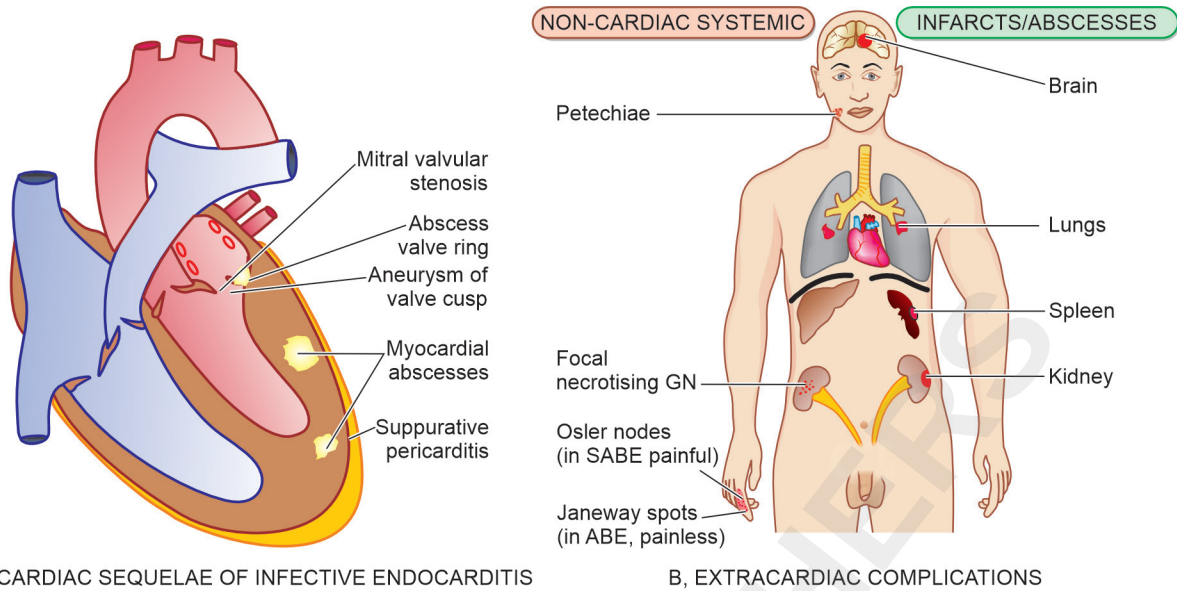


Figure 17.35 Complications and sequelae of infective endocarditis. (GN, glomerulonephritis; SABE, subacute bacterial endocarditis; ABE, acute bacterial endocarditis).

- v) Suppurative pericarditis
- vi) Cardiac failure from one or more of the foregoing complications

II. Extracardiac complications Since the vegetations in BE are typically friable, they tend to get dislodged due to rapid stream of blood and give rise to embolism which is responsible for very common and serious extracardiac complications. These are as follows:

- i) Emboli originating from the *left side of the heart* and entering the systemic circulation affect organs like the spleen, kidneys, and brain causing infarcts, abscesses and mycotic aneurysms.
- ii) Emboli arising from the *right side of the heart* enter pulmonary circulation and produce pulmonary abscesses.
- iii) *Petechiae* may be seen in the skin and conjunctiva due to either emboli or toxic damage to the capillaries.
- iv) In SABE, there are painful, tender nodules on the finger-tips of hands and feet called *Osler nodes*, while in ABE there is appearance of painless, non-tender subcutaneous maculopapular lesions on the pulp of the fingers called *Janeway lesions*. In either case, their origin is due to toxic or allergic inflammation of the vessel wall.
- v) *Focal necrotizing glomerulonephritis* is seen more commonly in SABE than in ABE. Occasionally diffuse glomerulonephritis may occur. Both these have their pathogenesis in circulating immune complexes (hypersensitivity phenomenon) (page 721).

CLINICAL FEATURES AND CRITERIA FOR DIAGNOSIS Most cases of BE present with fever. The acute form of BE is characterized by high grade fever, chills, weakness and malaise while the subacute form of the disease has non-specific manifestations like slight fever, fatigue, loss of weight and flu-like symptoms.

Although diagnosis of BE is confirmed by histological and microbiological examination of vegetation, clinical criteria to diagnose IE were first proposed in 1992 by Duke Endocarditis

Service (*Duke criteria*) which has undergone several modifications. Latest **modified Duke criteria (2023)** have been refined to include a few additional major and certain minor criteria based on advanced imaging, molecular microbiologic tests, and intraoperative surgical findings; these are in addition to previously described clinical, microbiological and laboratory parameters. A definite diagnosis requires 2 major, or 1 major + 3 minor, or 5 minor criteria. At present, highlights of major and minor criteria for diagnosis of IE are as under:

I. Major criteria

- i) *Microbiological* Blood culture positive for typical micro-organisms (sample taken >2 times, 12 hours apart); or positive PCR/other nucleic acid test for novel pathogens.
- ii) *Imaging* Echocardiography and/or CT showing vegetation, abscess, new prosthetic valve dehiscence, or paravalvular lesion.
- iii) *Surgical* Evidence of IE documented by direct inspection during heart surgery.

II. Minor criteria

- i) *Predisposition*, e.g. preexisting heart condition, intravenous drug use, previous history of IE.
- ii) *Fever*, i.e. temperature >38°C (or >100.4°F).
- iii) *Vascular phenomenon*, e.g. arterial emboli, septic pulmonary emboli, mycotic emboli, intracranial hemorrhage, conjunctival petechiae, Janeway lesions.
- iv) *Immunologic phenomenon*, i.e. glomerulonephritis, Osler nodes, rheumatoid factor.
- v) *Serologic positive test* for anti-ASO, immune complexes.
- vi) *Microbial evidence* by positive blood culture, but not meeting major criteria.

Treatment of BE with antibiotics in adequate dosage kills the bacteria, but complications and sequelae of healed endocardial lesions may occur even after successful therapy. The *causes of death* are cardiac failure, persistent infection, embolism to vital organs, renal failure and rupture of mycotic aneurysm of cerebral arteries.

SPECIFIC TYPES OF INFECTIVE ENDOCARDITIS

Besides BE, various other types of microbes may occasionally produce infective endocarditis which is named according to the etiologic agent causing it. These include the following:

1. Tuberculous endocarditis Though tubercle bacilli are bacteria, tuberculous endocarditis is described separately from the BE due to specific granulomatous inflammation found in tuberculosis. It is characterized by presence of typical tubercles on the valvular as well as mural endocardium and may form tuberculous thromboemboli.

2. Syphilitic endocarditis The endocardial lesions caused by *Treponema pallidum* have already been described in relation to syphilitic aortitis on page 434. The severest manifestation of cardiovascular syphilis is aortic valvular incompetence.

3. Fungal endocarditis Rarely, endocardium may be infected with fungi such as by *Candida albicans*, *Histoplasma capsulatum*, *Aspergillus*, *Mucor*, coccidioidomycosis, cryptococcosis, blastomycosis and actinomycosis. Opportunistic fungal infections like candidiasis and aspergillosis are seen more commonly in patients receiving long-term antibiotic therapy, intravenous drug abusers and after prosthetic valve replacement. Fungal endocarditis produces an appearance like that in BE but the vegetations are bulkier than BE.

SUMMARY Non-Rheumatic Endocarditis

Types

- **Libman-Sacks (atypical verrucous) endocarditis** Associated with collagen vascular diseases like SLE. Vegetations are small, granular, and multiple.
- **Non-bacterial thrombotic endocarditis (NBTE)** Characterized by sterile thrombotic vegetations, often seen in hypercoagulable states or chronic debilitating diseases.
- **Infective or bacterial endocarditis (IE or BE)** Occurs due to transient bacteremia, septicemia, and pyemia in predisposed individuals with underlying heart disease and impaired host defenses; characterized by large, friable vegetations.

Cardiac Vegetations (Compared with those in RHD)

- **Vegetations in RHD** Small, multiple, warty, gray-brown, translucent, firmly attached, generally produce permanent valvular deformity.
- **Libman-Sacks endocarditis** Small, granular, sterile vegetations; do not cause valve deformity.
- **NBTE vegetations** Sterile, thrombotic vegetations, brownish, and friable.
- **Vegetations in IE** Largest, friable, infected vegetations with eosinophilic cap and bacterial colonies.

Sites of Vegetations (versus RHD)

- **Vegetations in RHD** Occur along the line of closure. Follows direction of blood flow; accordingly, can be seen on atrial surface of AV valves, and ventricular surface of semilunar valves.
- **Libman-Sacks endocarditis** Mitral and tricuspid valve pockets; only vegetation that can be seen on both sides of valve leaflets or cusps.

- **NBTE vegetations** Primarily on the mitral valve, along line of closure; less often on aortic and tricuspid valves. Also, follows direction of blood flow; accordingly, can be seen on atrial surface of AV valves, and ventricular surface of semilunar valves.
- **Vegetations in IE** More common on the valves of the left heart (mitral and aortic valves), may also affect the right heart valves. Location is the same as rheumatic vegetations.

Complications

- **Cardiac** Valvular stenosis or insufficiency, perforation, rupture, aneurysm of valve leaflets, abscesses, myocardial abscesses, suppurative pericarditis, cardiac failure.
- **Extracardiac** Embolism leading to infarcts, abscesses, mycotic aneurysms in organs like spleen, kidneys, and brain; pulmonary abscesses; petechiae in skin and conjunctiva; Osler nodes and Janeway lesions; focal necrotizing glomerulonephritis.

VALVULAR DISEASES AND DEFORMITIES

Valvular diseases are various forms of congenital and acquired diseases which cause valvular deformities. Many of them result in cardiac failure. Rheumatic heart disease is the most common form of acquired valvular disease. Valves of the left side of the heart are involved much more frequently than those of the right side of the heart. The mitral valve is affected most often, followed in descending frequency, by the aortic valve, and combined mitral and aortic valves.

The valvular deformities may be of two types: stenosis and insufficiency:

- **Stenosis** is narrowing of the valvular opening from whatever cause. Resultantly, it fails to open fully and obstructs the forward flow of blood.
- **Insufficiency or incompetence or regurgitation** is due to damaged valvular cusps or their ring. The result is failure of the valve to close tightly and thus blood flows backward.

The *congenital valvular diseases* have already been listed and discussed (page 461). Here, various *acquired valvular diseases* that may deform the heart valves are listed below:

1. RHD, the commonest cause (page 474)
2. Infective endocarditis (page 481)
3. Non-bacterial thrombotic endocarditis (page 480)
4. Libman-Sacks endocarditis (page 480)
5. Syphilitic valvulitis (page 109)
6. Calcific aortic valve stenosis
7. Calcification of mitral annulus
8. Myxomatous degeneration (floppy valve syndrome)
9. Carcinoid heart disease

Out of this list, major forms of vegetative endocarditis involving the valves have already been described. Others along with the consequences of these valvular diseases in the form of stenosis and insufficiency of the heart valves are described below.

MITRAL STENOSIS

Mitral stenosis occurs in approximately 40–60% of all patients with RHD. About 70% of these patients are women. The latent period between rheumatic carditis and the development of symptomatic mitral stenosis is about two decades.

ETIOLOGY Most common causes are as under:

- i) RHD, the most common cause
- ii) Congenital parachute mitral valve
- iii) Severe mitral annular calcification
- iv) Libman-Sacks endocarditis

MORPHOLOGY The appearance of the mitral valve in stenosis varies according to the extent of involvement. Generally, the valve leaflets are diffusely thickened by fibrous tissue and/or calcific deposits, especially towards the closing margin. There are fibrous adhesions of mitral commissures (the areas where the two flaps of mitral valve join) and fusion and shortening of chordae tendineae (tendon-like cords of fibrous tissue that attach the AV valves to the ventricular papillary muscles). In less extensive involvement, the bases of the leaflets of mitral valve are mobile, while the free margins have puckered and thickened tissue with narrowed orifice; this is called as '*purse-string puckering*.' The more advanced cases have rigid, fixed and immobile diaphragm-like valve leaflets with narrow, slit-like or oval mitral opening, commonly referred to as '*buttonhole*' or '*fish-mouth*' mitral orifice (**Fig. 17.36, B, Fig. 17.37**).

EFFECTS In normal adults, the mitral orifice is about 5 cm². Symptomatic mitral stenosis develops if the valve opening is reduced to 1 cm² resulting in significant elevation of left atrial pressure from the normal of 12 mm Hg to about 25 mm Hg leading to dilatation of the left atrium. Elevated left atrial pressure, in turn, raises pressure in the pulmonary veins and capillaries, reducing the pulmonary function and causing exertional dyspnea which is the chief symptom of mitral stenosis. The effects of mitral stenosis can thus be summarized as under:

1. Dilatation and hypertrophy of the left atrium.
2. Normal-sized or atrophic left ventricle due to reduced inflow of blood.
3. Pulmonary hypertension resulting from passive backward transmission of elevated left atrial pressure which causes:
 - i) chronic passive congestion of the lungs,
 - ii) hypertrophy and dilatation of the right ventricle, and
 - iii) dilatation of the right atrium when right heart failure supervenes.

MITRAL INSUFFICIENCY

Mitral insufficiency is caused by RHD in about 50% of patients, but in contrast to mitral stenosis pure mitral insufficiency occurs more often in men (75%). Later, mitral insufficiency is associated with some degree of mitral stenosis.

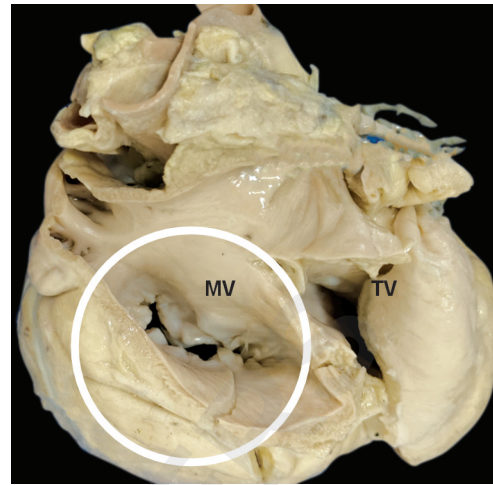


Figure 17.37 Mitral stenosis. A heart opened from the atrial side shows puckered mitral valve cusps with fish-mouth-like narrowing of orifice (within circle) with dilated left atrium. (The image contributed by Dr Sudheer Arava, Professor of Pathology, AIIMS, New Delhi).

ETIOLOGY All the causes of mitral stenosis may produce mitral insufficiency; following are additional causes:

- i) RHD, most common cause
- ii) Non-inflammatory calcification of mitral valve annulus (in the elderly)
- iii) Myxomatous transformation of mitral valve (floppy valve syndrome)
- iv) Healed endocarditis rupture
- v) Congenital
- vi) Rupture of a leaflet or papillary muscle post-MI

MORPHOLOGY Appearance of the mitral valve in insufficiency varies according to the underlying cause. Rheumatic process produces rigidity, deformity and retraction of the valve leaflets and fusion of commissures as well as shortening and fusion of chordae tendineae (**Fig. 17.36, C**).

- In *myxomatous degeneration* of the mitral valve leaflets (floppy valve syndrome) (described on page 488), there is prolapse of one or both leaflets into the left atrium during systole.
- In *non-inflammatory calcification* of mitral annulus seen in the aged, there is irregular, stony-hard, bead-like thickening in the region of mitral annulus without any associated inflammatory changes. It is thought to reflect degenerative changes of aging.

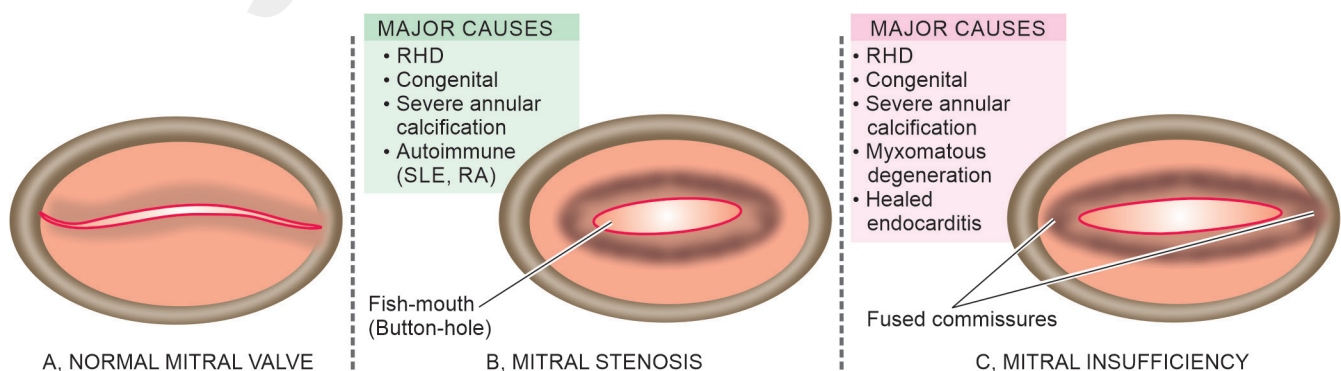


Figure 17.36 Mitral valve disease. Normal mitral valve (A) contrasted with mitral stenosis (B) and mitral insufficiency (C).

EFFECTS Regurgitant mitral orifice produces progressive increase in left ventricular end-diastolic volume as well as pressure since the left ventricle cannot empty completely. This results in a rise in left atrial pressure and dilatation. Because of left atrial hypertension, pulmonary hypertension occurs resulting in pulmonary edema and right heart failure. In symptomatic cases of mitral insufficiency, the major symptoms are related to decreased cardiac output (e.g. fatigue and weakness) and due to pulmonary congestion (e.g. exertional dyspnea and orthopnea), but the features are less well marked than in mitral stenosis. The effects of mitral insufficiency are summarized as under:

1. Dilatation and hypertrophy of the left ventricle.
2. Marked dilatation of the left atrium.
3. Features of pulmonary hypertension such as:
 - i) chronic passive congestion of the lungs,
 - ii) hypertrophy and dilatation of the right ventricle, and
 - iii) dilatation of the right atrium when right heart failure supervenes.

AORTIC STENOSIS

Aortic stenosis is the most common valvular lesion in adults and comprises about one-fourth of all patients with chronic valvular heart disease. About 80% patients of symptomatic aortic stenosis are males.

ETIOLOGY It is of two main types: non-calcific and calcific type; the latter is more common.

i) Calcific aortic stenosis Calcific aortic stenosis is the more common type. Its various causes are healing of valve by scarring followed by calcification of aortic valve such as in RHD, bacterial endocarditis, *Brucella* endocarditis, Mönckeberg calcific aortic stenosis, and familial hypercholesterolemia xanthomatosis.

ii) Non-calcific aortic stenosis The most common cause of non-calcific aortic stenosis is chronic RHD. Other causes are congenital valvular and subaortic stenosis, congenitally bicuspid aortic valve and radiation exposure.

MORPHOLOGY The aortic cusps show characteristic fibrous thickening and calcific nodularity of the closing edges. Calcified nodules are often found in the sinuses of Valsalva. In rheumatic aortic stenosis, the commissures are fused and calcified, while in non-rheumatic aortic stenosis there is no commissural fusion (**Fig. 17.38, B**).

EFFECTS Aortic stenosis becomes symptomatic when the valve orifice is reduced to 1 cm² from its normal 3 cm². The

symptoms appear many years later when the heart cannot compensate and the stenosis is quite severe. The major effect of aortic stenosis is obstruction to the outflow resulting in concentric hypertrophy of the left ventricle. Later, when cardiac failure supervenes, there is dilatation as well as hypertrophy of the left ventricle (eccentric hypertrophy) (page 456).

The *three cardinal symptoms* of aortic stenosis are: exertional dyspnea, angina pectoris and syncope:

- *Exertional dyspnea* results from elevation of pulmonary capillary pressure.
- *Angina pectoris* usually results from elevation of pulmonary capillary pressure and usually develops due to increased demand of hypertrophied myocardial mass.
- *Syncope* results from accompanying coronary insufficiency. Sudden death may also occur in an occasional case of aortic stenosis.

AORTIC INSUFFICIENCY

About three-fourth of all patients with pure or predominant aortic insufficiency are men while women with predominant aortic insufficiency have often associated rheumatic mitral valve disease too.

ETIOLOGY Major causes are as under:

- i) Chronic RHD is most common, seen in 75% cases (along with other valvular lesions)
- ii) Congenital bicuspid valve
- iii) Myxomatous degeneration (floppy valve syndrome) and Marfan syndrome
- iv) Infective endocarditis and syphilis
- v) Cystic medial degeneration
- vi) Traumatic rupture of the valve cusps
- vii) Ankylosing spondylitis
- viii) Hypertension

MORPHOLOGY The aortic valve cusps are thickened, deformed and shortened and fail to close. Generally, there is distension and distortion of the ring (**Fig. 17.38, C**).

EFFECTS As a result of regurgitant aortic orifice, there is an increase in the left ventricular end-diastolic volume. This leads to hypertrophy and dilatation of the left ventricle producing massive cardiac enlargement so that the heart may weigh as much as 1,000 g. Failure of the left ventricle increases the pressure in the left atrium and eventually pulmonary hypertension and right heart failure occurs.

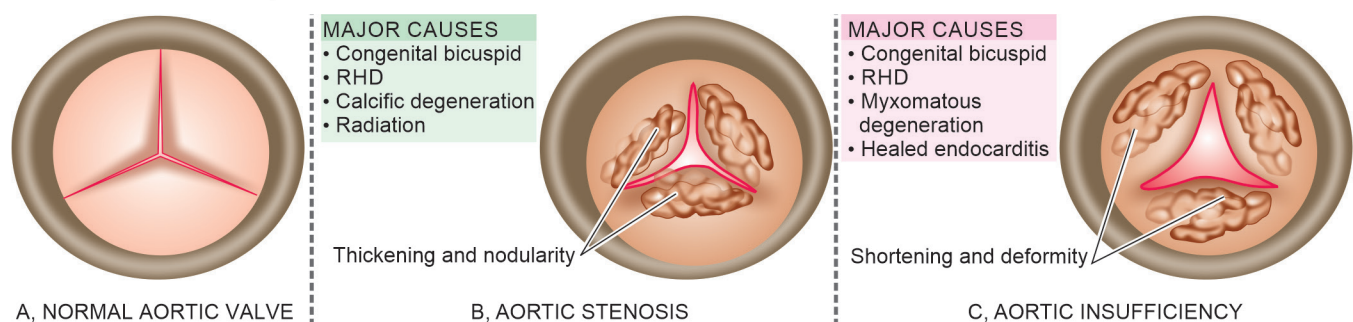


Figure 17.38 Aortic valve diseases. Normal aortic valve (A) contrasted with aortic stenosis (B) and aortic insufficiency (C).

MYXOMATOUS DEGENERATION OF MITRAL VALVE (MITRAL VALVE PROLAPSE)

Myxomatous or mucoid degeneration of the valves of the heart is a peculiar condition occurring in young patients between the age of 20 and 40 years and is more common in women. This condition is common and seen in 5% of adult population. The condition is also known by other synonyms like '*floppy valve syndrome*' or '*mitral valve prolapse*'.

ETIOLOGY Though the exact cause is unknown, in some cases it may be related to genetically determined collagen disorder. Association with Marfan syndrome has been observed in 90% of patients. Others have noted myxomatous degeneration in cases of Ehlers-Danlos syndrome and in myotonic dystrophy. However, the myxomatous valvular changes seen in the aged patients are not related to this entity.

MORPHOLOGY Any cardiac valve may be involved but mitral valve is affected most frequently. The disease is usually the most severe and most common in the *posterior leaflet of the mitral valve*. The affected leaflet shows either excessive or redundant leaflet tissue, which is opaque white, soft and floppy. The cut section of the valve reveals mucoid or myxoid appearance. A significant feature is the ballooning or aneurysmal protrusion of the affected leaflet and hence the name '*mitral valve prolapse*' and '*floppy valve syndrome*'.

Microscopically, the enlarged cusp shows loose connective tissue with abundant mucoid or myxoid material due to abundance of mucopolysaccharide.

EFFECTS Usually the condition does not produce any symptoms or significant valvular dysfunction. The condition is recognized during life by the characteristic mid-systolic click followed by a systolic murmur due to mildly incompetent mitral valve caused by the mitral valve prolapse into atrium during mid systole. Occasionally, complications may develop such as superimposed infective endocarditis, mitral insufficiency and arrhythmias. Rarely, sudden death from serious ventricular arrhythmias may occur.

SUMMARY Valvular Diseases and Deformities

Common Cardiac Valvular Disorders

- Rheumatic heart disease (RHD)
- Infective endocarditis
- Non-bacterial thrombotic endocarditis
- Libman-Sacks endocarditis
- Syphilitic valvulitis
- Calcific aortic valve stenosis
- Calcification of mitral annulus
- Myxomatous degeneration (Floppy valve syndrome)
- Carcinoid heart disease

Mitral Stenosis

- Occurs in 40–60% of patients with RHD, predominantly in women.
- **Causes** Include RHD, congenital parachute mitral valve, severe mitral annular calcification, and Libman-Sacks endocarditis.

- **Morphology** Thickened valve leaflets, fibrous adhesions, fusion and shortening of chordae tendineae, and narrowed orifice ('fish-mouth' appearance).
- **Effects** Elevated left atrial pressure, dilatation of the left atrium, pulmonary hypertension, and right heart failure.

Mitral Insufficiency

- **Causes** RHD in about 50% of patients, more common in men. Other causes include, non-inflammatory calcification of mitral valve annulus, myxomatous transformation, healed endocarditis rupture, congenital defects, and post-MI papillary muscle rupture.
- **Morphology** Rigidity, deformity, and retraction of valve leaflets, prolapse of leaflets in myxomatous degeneration, calcified mitral annulus.
- **Effects** Dilatation and hypertrophy of the left ventricle marked dilatation of the left atrium, pulmonary hypertension, and right heart failure.

Aortic Stenosis

- Most common valvular lesion in adults, predominantly in males.
- **Causes** Include calcific types (RHD, bacterial endocarditis, Brucella endocarditis, Mönckeberg calcific aortic stenosis, familial hypercholesterolemic xanthomatosis), and non-calcific (chronic RHD, congenital valvular and subaortic stenosis, bicuspid aortic valve, radiation exposure).
- **Morphology** Fibrous thickening and calcific nodularity of valve cusps, fusion of commissures in rheumatic type.
- **Effects** Concentric hypertrophy of the left ventricle, exertional dyspnea, angina pectoris, syncope, and potential sudden death.

Aortic Insufficiency

- Seen in 75% of patients with chronic RHD, mostly men.
- **Causes** Include RHD, congenital bicuspid valve, myxomatous degeneration, Marfan syndrome, infective endocarditis, syphilis, cystic medial degeneration, traumatic rupture, ankylosing spondylitis, and hypertension.
- **Morphology** Thickened, deformed, and shortened valve cusps along with distended and distorted aortic ring.
- **Effects** Hypertrophy and dilatation of the left ventricle, massive cardiac enlargement, elevated left atrial pressure, pulmonary hypertension, and right heart failure.

OTHER MYOCARDIAL DISEASES

Involvement of the myocardium occurs in all the three major forms of cardiac diseases discussed already, i.e. ischemic heart disease, hypertensive heart disease and rheumatic heart disease. In addition, there are two other broad groups of isolated myocardial diseases:

- I. *Myocarditis*, i.e. inflammatory involvement of the myocardium.
- II. *Cardiomyopathy*, i.e. a non-inflammatory myocardial involvement due to several etiologies including genetic causes.

MYOCARDITIS

Inflammation of the heart muscle is called myocarditis. It is a rather common form of heart disease that can occur at any age. Its exact incidence is difficult to ascertain as the histological

examination has been largely confined to autopsy material. Reports from different studies have estimated the incidence of myocarditis in 1 to 4% of all autopsies.

Currently commonly used is *etiological classification* given in **Table 17.9**. According to this classification, myocarditis is divided into 4 main etiologic types described below.

I. INFECTIVE MYOCARDITIS

Several infectious agents such as bacteria, viruses, protozoa, parasites, fungi, rickettsiae and spirochetes may cause myocarditis by direct invasion or by their toxins. Some of the common forms are described below.

VIRAL MYOCARDITIS This is the most common cause among infectious myocarditis. Some of the common examples are adenoviruses, coxsackievirus, HIV, and hepatitis C. Cardiac involvement occurs in about 5% of viral infections. Viral myocarditis usually appears after a few days to a few weeks of viral infection elsewhere in the body. The damage to the myocardium is caused either by direct viral cytotoxicity or by cell-mediated immune reaction. Regardless of the type of virus, the pathological changes are similar.

Grossly, the myocardium is pale and flabby with dilatation of the chambers. There may be focal or patchy areas of necrosis.

Histologically, there are changes of acute myocarditis. Initially, there is edema and infiltration of the interstitial tissue by neutrophils and lymphocytes. Later, there is necrosis of individual myocardial fibers and the infiltrate consists of lymphocytes and macrophages (**Fig. 17.39**).

BACTERIAL MYOCARDITIS Most bacterial infections during systemic disease may rarely involve myocardium. However, diphtheria specifically affects heart in about half the cases and cardiac involvement is the most common cause of death in diphtheria. As already discussed, acute bacterial endocarditis may sometimes cause bacterial myocarditis (page 482).

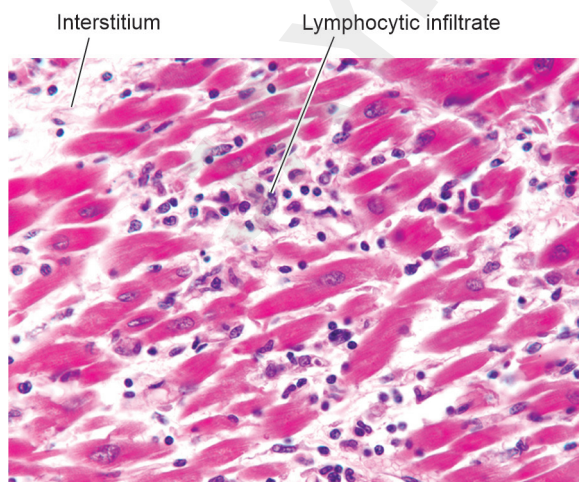


Figure 17.39 Viral myocarditis. It shows lymphocytic inflammatory infiltrate in the interstitium and destroying some of myocardial fibers. (Reproduced with permission from *Atlas of Histopathology* by Ivan Damjanov 2012, Jaypee Brothers Medical Publishers Pvt Ltd, New Delhi).

TABLE 17.9 Etiologic classification of myocarditis.

I. INFECTIVE MYOCARDITIS	
	1. Viral myocarditis 2. Bacterial myocarditis 3. Granulomatous myocarditis 4. Syphilitic myocarditis 5. Rickettsial myocarditis 6. Protozoal myocarditis 7. Helminthic myocarditis 8. Fungal myocarditis
II. MYOCARDITIS IN CONNECTIVE TISSUE DISEASES	
	1. Lupus erythematosus 2. Rheumatoid arthritis 3. Polyarteritis nodosa 4. Dermatomyositis 5. Scleroderma
III. MISCELLANEOUS TYPES OF MYOCARDITIS	
	1. Iatrogenic (irradiation, cardiovascular surgery, drugs) 2. Metabolic derangements (uremia, hypokalemia, shock)
IV. IDIOPATHIC (FIEDLER) MYOCARDITIS	
	Diffuse type/Giant cell idiopathic type

Grossly, there are either abscesses in the myocardium or there is diffuse myocardial involvement.

Microscopically, the exudate chiefly consists of neutrophils, mixed with lymphocytes, plasma cells and macrophages (**Fig. 17.40**). There may be foci of myocardial degeneration and necrosis; later there may be areas of healing by fibrosis.

GRANULOMATOUS MYOCARDITIS Tuberculosis, brucellosis and tularemia are some examples of bacterial infections characterized by granulomatous inflammation in the myocardium. Sarcoidosis, though not a bacterial infection, has histological resemblance to other granulomatous myocarditis. Tuberculous myocarditis is rare and occurs either by hematogenous spread or by extension from tuberculous pericarditis (**Fig. 17.41**). The condition must be distinguished from idiopathic granulomatous (giant cell) myocarditis (described later).

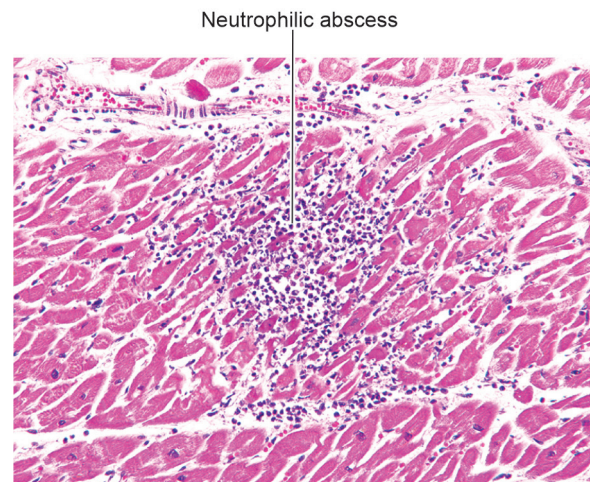


Figure 17.40 Bacterial myocarditis. There are foci of neutrophilic infiltrate in the myocardium forming a small abscess. (Reproduced with permission from *Atlas of Histopathology* by Ivan Damjanov 2012, Jaypee Brothers Medical Publishers Pvt Ltd, New Delhi).

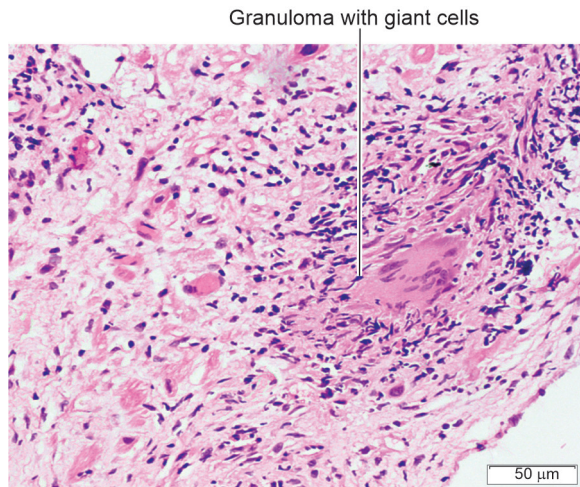


Figure 17.41 Granulomatous myocarditis. A focus of chronic granulomatous inflammation in the myocardium surrounded by mononuclear cells. (The image contributed by Dr Sudheer Arava, Professor of Pathology, AIIMS, New Delhi).

SYPHILITIC MYOCARDITIS Syphilitic involvement of the myocardium may occur in two forms—a *gummatous lesion* consisting of granulomatous inflammation which is more common, and a *primary non-specific myocarditis* which is rare. The syphilitic gumma in the myocardium may be single or multiple and may be grossly discernible. The gummas may affect the conduction system of the heart.

RICKETTSIAL MYOCARDITIS Myocarditis occurs quite frequently in scrub typhus (*R. tsutsugamushi*) and Rocky Mountain typhus fever caused by spotted rickettsii.

Microscopically, there is interstitial edema and focal or patchy infiltration by inflammatory cells which include lymphocytes, plasma cells, macrophages, mast cells and eosinophils but necrosis and degeneration are generally not present.

PROTOZOAL MYOCARDITIS Chagas disease and toxoplasmosis are the two protozoal diseases causing myocarditis. Chagas disease caused by *Trypanosoma cruzi* frequently attacks myocardium besides involving the skeletal muscle and the central nervous system. Toxoplasmosis is caused by intracellular protozoan, *Toxoplasma gondii*, sometimes causes myocarditis in children and adults.

Microscopically, both these conditions show focal degeneration and necrosis of the myocardium, edema and cellular infiltrate consisting of histiocytes, plasma cells, lymphocytes and a few polymorphs. The organisms are found in the muscle fibers.

HELMINTHIC MYOCARDITIS *Echinococcus granulosus* and *Trichinella spiralis* are the two intestinal helminths which may cause myocarditis. *Echinococcus* rarely produces hydatid cyst in the myocardium while the larvae of *Trichinella* in trichinosis causes heavy inflammation in the myocardium as well as in the interstitial tissue.

FUNGAL MYOCARDITIS Patients with immunodeficiency, cancer and other chronic debilitating diseases are more prone to develop fungal myocarditis. These include candidiasis, aspergillosis, blastomycosis, actinomycosis, cryptococcosis, coccidioidomycosis and histoplasmosis.

II. MYOCARDITIS IN CONNECTIVE TISSUE DISEASES

Inflammatory involvement of the myocardium occurs in several connective tissue diseases such as rheumatoid arthritis, lupus erythematosus, rheumatoid arthritis, polyarteritis nodosa, dermatomyositis and scleroderma. The pathological changes in the heart muscle are like the changes seen in other organs in these conditions as described elsewhere in relevant chapters.

III. MISCELLANEOUS TYPES OF MYOCARDITIS

Apart from the above forms of myocarditis, miscellaneous group consists of myocarditis caused by a variety of agents such as drugs, radiation therapy and metabolic derangements.

IATROGENIC Certain therapeutic modalities can lead to inflammation of myocardium. For example,

- *Drugs* like chemotherapeutic agents (doxorubicin and daunorubicin) used for the treatment of various cancers.
- *Radiation therapy* used for treatment of lung and mediastinal tumors as well as cardiovascular surgeries.

METABOLIC DERANGEMENTS Uremia, hypokalemia and shock are associated with degeneration and necrosis of the myocardial fibers, edema of the interstitial tissue and non-specific inflammatory reaction.

IV. IDIOPATHIC (FIEDLER) MYOCARDITIS

Idiopathic or Fiedler myocarditis is an isolated myocarditis unaccompanied by inflammatory changes in the endocardium or pericardium and occurs without an apparent cause. The condition is rapidly progressive and causes sudden severe cardiac failure or sudden death.

Grossly, the heart is soft and flabby. The cardiac chambers are generally dilated and sometimes show hypertrophy. There are yellow-gray focal lesions throughout the myocardium. Mural thrombi are commonly present.

Histologically, two forms of idiopathic myocarditis are described: diffuse type and giant cell (idiopathic granulomatous) type.

i) **Diffuse type** is more common of the two. It is characterized by diffuse non-specific inflammatory infiltrate consisting of lymphocytes, plasma cells, macrophages, eosinophils and a few polymorphs in the interstitial tissue without formation of granulomas. Late stage shows healing by fibrosis.

ii) **Giant cell type or idiopathic granulomatous type** is characterized by formation of non-caseating granulomas consisting of macrophages, lymphocytes, plasma cells and multinucleate giant cells. The giant cells are of foreign body or Langhans type or of myogenic origin. The granulomas do not show the presence of acid-fast bacilli or spirochaetes. Some have suggested relationship of this condition with sarcoidosis, but sarcoid granulomas are known to occur in the myocardium secondary to generalized sarcoidosis.

CARDIOMYOPATHY

DEFINITION AND CLASSIFICATION

Cardiomyopathy (CMP) literally means disease of the heart muscle, but the term was originally coined to restrict its usage to *myocardial disease of unknown cause*. However, the term cardiomyopathy has been loosely used by various workers for certain myocardial diseases of known etiology as well, e.g. alcoholic CMP, amyloid CMP, ischemic CMP, etc.

CMPs are a heterogeneous group of myocardial diseases which are:

- associated with mechanical and/or electrical dysfunction,
- have morphological features in the myocardium, and
- are due to genetic causes.

Based on this definition, a classification of CMPs and their subtypes is given in **Table 17.10**. Pathophysiologically, there are three categories of CMPs (**Fig. 17.42**):

- Dilated (congestive) cardiomyopathy
- Hypertrophic cardiomyopathy
- Restrictive or obliterative or infiltrative cardiomyopathy

I. DILATED (CONGESTIVE) CMP

This type of CMP is characterized by gradually progressive cardiac failure along with dilatation of all the four chambers of the heart. The condition occurs more often in adults and the average survival from onset to death is less than 5 years.

ETIOLOGY A few hypotheses based on associations with the following conditions have been proposed:

- Possible association of *viral myocarditis* (especially coxsackievirus B) has been noted based on presence of viral nucleic acids in the myocardium in dilated CMP.
- Association with *toxic damage* from cobalt and chemotherapy with doxorubicin and other anthracyclines is implicated in some cases.
- Genetic basis* can be established in 20–50% cases of dilated CPM due to inherited mutations, especially in young people and those with history of familial occurrence. Mutations in one or more of over 50 genes have been described; some common mutations in genes encoding the following proteins are as follows:
 - Cytoskeletal proteins (e.g. cardiac actin and desmin)
 - Sarcomere proteins (e.g. cardiac troponin-T and I, titin)
 - Nuclear proteins (e.g. lamin A and lamin C)
 - Contractile proteins (e.g. myosin)

TABLE 17.10 Classification of cardiomyopathy.

I.	DILATED (OR CONGESTIVE) CARDIOMYOPATHY
	Variant form: Arrhythmogenic right ventricular cardiomyopathy/dysplasia
II.	HYPERTROPHIC CARDIOMYOPATHY
	1. Obstructive 2. Non-obstructive type
III.	RESTRICTIVE (OR INFILTRATIVE) CARDIOMYOPATHY
	1. Cardiac amyloidosis 2. Endocardial fibroelastosis 3. Endomyocardial fibrosis 4. Löffler endocarditis 5. Other forms (sarcoidosis, carcinoid syndrome, scleroderma)

- Cell membrane and membrane-linked proteins (e.g. dystrophin in Duchenne dystrophy)
- Mitochondrial proteins (e.g. enzymes involved in oxidative phosphorylation)
- Conduction system proteins accounting for the “channelopathies”
- Chronic alcoholism* has been found associated with dilated cardiomyopathy. It may be due to thiamine deficiency induced by alcohol and resulting in beriberi heart disease (page 288). This is referred to as ‘alcoholic CMP’. However, moderate consumption of alcohol provides some cardioprotection against IHD by raising HDL cholesterol. Another form of alcoholic CMP is associated with consumption of large quantities of beer (*beer drinkers’ myocardiosis*). Cobalt is added to the beer to improve the appearance of foam, but is blamed to cause direct toxic injury to the heart in this condition.
- Peripartum association* has been observed in some cases. Poorly nourished women may develop this form of CMP within a month before or after delivery (peripartum CMP).

Grossly, the heart is enlarged and increased in weight (up to 1,000 g). The most characteristic feature is the prominent dilatation of all the four chambers, giving the heart a typical globular appearance. Thickening of the ventricular walls even if present is masked by the ventricular dilatation (**Fig. 17.42, B**). The endocardium is thickened, and mural thrombi are often found in the ventricles and atria (**Fig. 17.43**). The cardiac valves are usually normal.

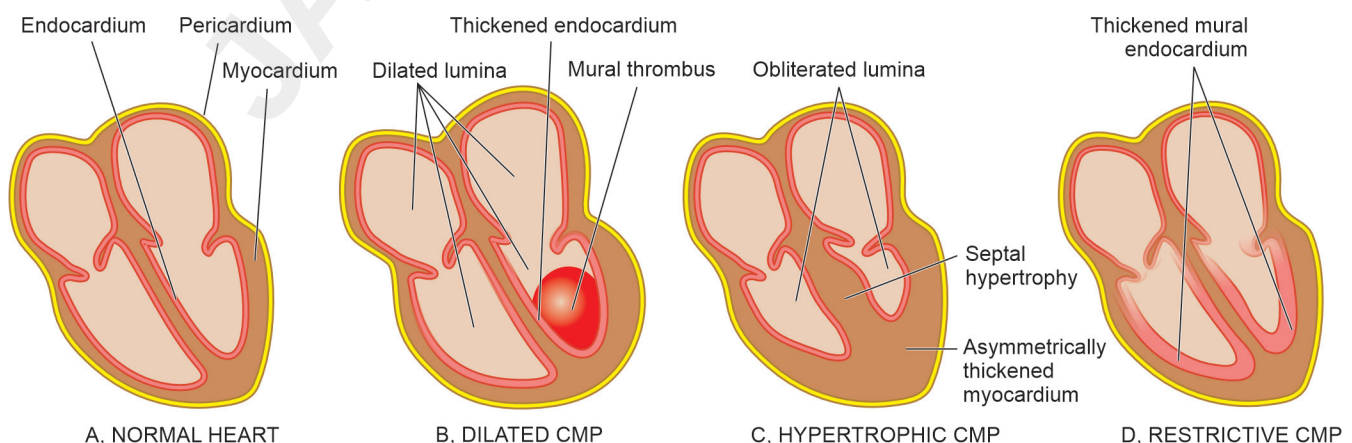


Figure 17.42 Three pathophysiologic forms of idiopathic cardiomyopathies. (CMP, cardiomyopathy).

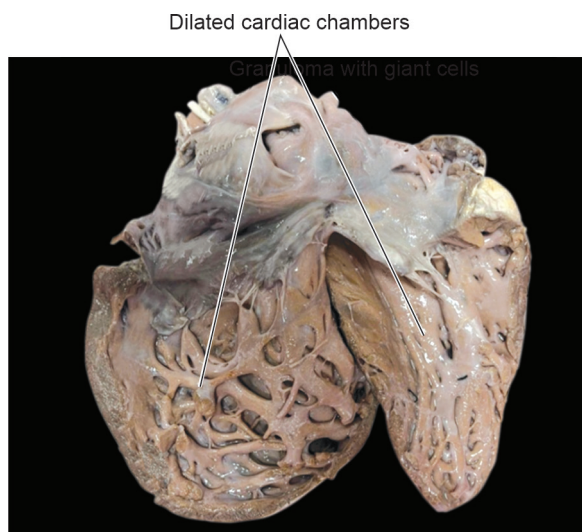


Figure 17.43 Dilated cardiomyopathy. The heart is enlarged, heavy and shows dilatation of cardiac chambers. (The image contributed by Dr Sudheer Arava, Professor of Pathology, AIIMS, New Delhi).

Microscopically, the endomyocardial biopsies or autopsy examination of the heart reveal non-specific and variable changes. There may be hypertrophy of some myocardial fibers and atrophy of others. Sometimes degenerative changes and small areas of interstitial fibrosis are found with focal mononuclear inflammatory cell infiltrate.

ARRHYTHMOGENIC CMP

As the name indicates, arrhythmogenic cardiomyopathy/dysplasia is characterized by ventricular arrhythmias in the young which can increase the risk of sudden cardiac arrest and sudden death in teens and young adults such as athletes. Its incidence varies from 1 in 1,000 to 1 in 5,000 people. More often, it affects the right ventricle (arrhythmogenic right ventricular dysplasia/CMP) but may involve left ventricle as well.

ETIOLOGY AND PATHOGENESIS Following facts are known about the causes of arrhythmogenic CMP:

- Family history* of this condition is present in 30–50% of cases. Pattern of inheritance is more commonly autosomal dominant and less often autosomal recessive.
- About 60% of cases have *genetic mutation*; at least 13 genes have been identified that can have mutation. Most common is mutation in gene coding for desmosome protein.
- A few *other factors* related to this condition are other congenital right ventricular abnormalities, viral or other inflammatory myocarditis, etc.

Pathogenesis is explained by the replacement of ventricular tissue with fat and fibrous tissue that interferes with conduction system of the heart.

Grossly, the heart is enlarged and increased in weight.

Microscopically, there is fibrofatty replacement of the ventricular myocardial muscle, more often right and less often left side. Both ventricles are involved in about 40% cases. There may be mild inflammation and rarely myocyte necrosis.

II. HYPERTROPHIC CMP

This form of CMP is known by various synonyms like asymmetrical hypertrophy, hypertrophic subaortic stenosis and Teare disease. HCM occurs more frequently between the age of 25 and 50 years. It is often asymptomatic, but becomes symptomatic due to heavy physical activity causing dyspnea, angina, congestive heart failure and even sudden death.

ETIOLOGY Following factors have been implicated:

- Autosomal dominant inheritance* of the disease is available in about half the cases suggesting genetic factors in its causation.
- Inherited mutations* in genes encoding for sarcomere proteins have been reported in a much larger number of cases of hypertrophic CMP than those of dilated CMP. Particularly implicated are the mutations in heavy and light chains of cardiac b-myosin, troponin-I and troponin-T. The condition may result from *myocardial ischemia* resulting in fibrosis of the intramyocardial arteries and compensatory hypertrophy.

Grossly, the characteristic features are cardiac enlargement, increase in weight, normal or small ventricular cavities and myocardial hypertrophy. The hypertrophy of the myocardium is typically asymmetrical and affects the interventricular septum more than the free walls of the ventricles (**Fig. 17.42, C**). This asymmetric septal hypertrophy may be confined to the apical region of the septum (*non-obstructive type*) or may extend up to the level of the mitral valve causing obstruction to left ventricular outflow in the form of subaortic stenosis (*obstructive type*). The designation of *rhabdomyoma of the septum* has also been applied in the past to this form of CMP.

Microscopically, the classical feature is the myocardial cell disorganization in the ventricular septum. The bundles of myocardial fibers are irregularly and haphazardly arranged rather than the usual parallel pattern and are separated by bands of interstitial fibrous tissue. The individual muscle cells show hypertrophy and large prominent nuclei (**Fig. 17.44**).

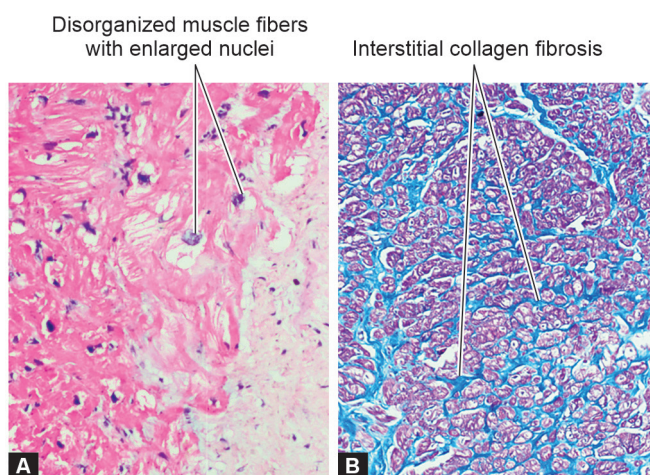


Figure 17.44 Hypertrophic cardiomyopathy. A, There is disorganization of myocardial fibers with nuclear enlargements. B, Masson Trichrome stain for collagen shows interstitial fibrosis. (The images contributed by Dr Sudheer Arava, Professor of Pathology, AIIMS, New Delhi).

III. RESTRICTIVE (OBLITERATIVE OR INFILTRATIVE) CMP

This form of CMP is characterized by restriction in ventricular filling due to reduction in ventricular volume (**Fig. 17.42, D, Fig. 17.45**). The common feature in this heterogeneous group of conditions producing restrictive cardiomyopathy is abnormal diastolic function. Restrictive CMP includes the following entities:

1. Cardiac Amyloidosis

Amyloidosis of the heart may occur in any form of systemic amyloidosis or may occur as isolated organ amyloidosis in amyloid of aging and result in subendocardial deposits. The deposit of amyloid occurs in the interstitium and replaces and constricts the myocardial fibers (page 163).

2. Endocardial Fibroelastosis

Among the restrictive CMP, worldwide this is the most common type, occurring predominantly in infants and children under 2 years of age and less often in adults. The *infantile form* is clinically characterized by sudden breathlessness, cyanosis, cardiac failure and death whereas the symptoms in the *adult form* last for longer duration.

ETIOLOGY Exact etiology is not known.

- i) The disease could be primary or secondary to various congenital heart diseases such as aortic stenosis or atresia.
- ii) It could be because of intrauterine exposure to viral infection, e.g. mumps.
- iii) It may occur sporadically or inherited as x-linked or autosomal recessive genetic trait.
- iv) Genetic mutation in gene encoding mitochondrial inner membrane protein, tafazzin (TAZ), has been identified.

Grossly, the characteristic feature is the diffuse or patchy, rigid, pearly-white thickening of the mural endocardium. Left ventricle is predominantly involved, followed in decreasing frequency, by the left atrium, right ventricle and right atrium. Quite often, the valves, especially of the left heart, are affected. Some cases contain mural thrombi. Enlargement of the heart is present and is mainly due to left ventricular hypertrophy, but the volume of the chamber is decreased.

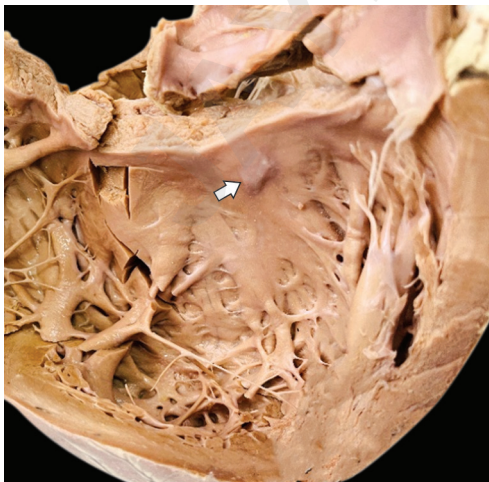


Figure 17.45 Restrictive cardiomyopathy. There is marked thickening and nodularity of the ventricular endocardium (arrow). (The image contributed by Dr Sudheer Arava, Professor of Pathology, AIIMS, New Delhi).

Microscopically, typical finding is the proliferation of the collagen and elastic tissue (fibroelastosis) comprising the thickened endocardium. Fibroelastosis generally does not extend into the subjacent myocardium. The lesion is devoid of inflammatory cells.

3. Endomyocardial Fibrosis

This form of restrictive cardiomyopathy is a tropical condition prevalent in Africa, especially in Uganda and Nigeria, but some cases occur in South India, Sri Lanka, Malaysia and tropical South America. It is seen in children and young adults. The clinical manifestations consist of congestive heart failure of unknown cause just as in adult variety of endocardial fibroelastosis.

ETIOLOGY The etiology of the condition remains obscure, but the geographic distribution suggests the role of certain factors like malnutrition, viral infections and heavy consumption of banana (rich in serotonin).

Grossly, the heart may be normal sized or hypertrophied, but the volume of the affected chambers is diminished due to fibrous scarring. Endomyocardial fibrosis is characterized by fibrous scarring of the ventricular endocardium that extends to involve the inner third of the myocardium. The atrioventricular valve leaflets are often affected but the semilunar valves are uninvolved. Mural thrombi may be present.

Microscopically, the endocardium and parts of inner third of the myocardium show destruction of normal tissue and replacement by fibrous tissue. The condition differs from endocardial fibroelastosis in having mononuclear inflammatory cell infiltrate and lacking in elastic tissue.

4. Löffler Endocarditis

Also known by the more descriptive term of 'fibroplastic parietal endocarditis with peripheral blood eosinophilia', the condition is considered by some as a variant of endomyocardial fibrosis. However, it differs from the latter in the following respects:

- i) There is generally peripheral blood eosinophilic leukocytosis.
- ii) The inflammatory infiltrate in the endocardium and in the part of affected myocardium chiefly consists of eosinophils. These eosinophils release toxic product (major basic protein—MBP) which is responsible for the myocardial damage and scarring.
- iii) The condition has a worse prognosis.

5. Carcinoid Heart Disease

Besides the above, restrictive cardiomyopathy may result from various diverse causes such as carcinoid syndrome, myocardial sarcoidosis, and scleroderma.

ETIOLOGY AND PATHOGENESIS Carcinoid syndrome developing in patients with extensive hepatic metastases from a carcinoid tumor is characterized by cardiac manifestations in about half the cases (page 628). The lesions are characteristically located in the valves and endocardium on the right side of the heart. Carcinoid heart disease occurs when large amounts of vasoactive substances secreted by the tumor such as serotonin and prostaglandins reach the right side of the heart because of their reduced metabolism in the liver due to extensive hepatic

metastases of the carcinoid tumor. The left side of the heart is generally spared because lungs metabolize and inactivate these substances on passage of the blood through the lungs.

MORPHOLOGY In majority of cases, the lesions are *limited to the right side of the heart*. Both pulmonary and tricuspid valves as well as the endocardium of the right chambers show characteristic cartilage-like fibrous plaques. Similar plaques may occur on the intima of the great veins, the coronary sinus and the great arteries. Occasionally, the lesions may be found on the left side of the heart.

EFFECTS Thickening and contraction of the cusps and leaflets of the valves of the outflow tracts of the right heart result mainly in pulmonary stenosis and tricuspid regurgitation, and to a lesser extent, pulmonary regurgitation and tricuspid stenosis.

SUMMARY Other Myocardial Diseases

Myocarditis and its Types

Inflammatory involvement of the myocardium from various etiologies.

- **Infective Myocarditis** Causes include viral (e.g. adenoviruses, coxsackievirus, HIV, hepatitis C), bacterial (e.g. diphtheria, tuberculosis), protozoal (e.g. Chagas disease, toxoplasmosis), helminthic (e.g. *Trichinella spiralis*), and fungal (e.g. candidiasis, aspergillosis).
- **Myocarditis in connective tissue diseases** Associated with rheumatoid arthritis, lupus erythematosus, polyarteritis nodosa, dermatomyositis, and scleroderma.
- **Miscellaneous types** Includes iatrogenic causes (e.g. drugs, radiation therapy) and metabolic derangements (e.g. uremia, hypokalemia, shock).
- **Idiopathic (Fiedler) myocarditis** Unknown causes, possibly immune-mediated; characterized by diffuse non-specific inflammatory infiltrate, giant cells, and granulomas.

Morphologic Features and Effects of Myocarditis

- **Infective Myocarditis** Myocardial inflammation, necrosis, and degeneration with infiltrates (e.g. neutrophils, lymphocytes, eosinophils). Clinical effects include heart failure, arrhythmias, chest pain, fatigue, and dyspnea; may lead to sudden cardiac death.
- **Myocarditis in connective tissue diseases** Inflammatory infiltrates in the myocardium like other organs affected by the disease. Clinical effects vary but may include heart failure, arrhythmia, and pericarditis.
- **Miscellaneous types** Myocardial degeneration, necrosis, and interstitial edema with non-specific inflammatory reactions. Clinical effects include heart failure, arrhythmia, and other complications based on the underlying cause.
- **Idiopathic (Fiedler) myocarditis** Rapidly progressive cardiac failure, arrhythmias, and sudden death.

Cardiomyopathy (CMP) and its Types

Heart diseases associated with mechanical and/or electrical dysfunction, having morphological features in the myocardium; due to several causes which are frequently genetic.

- **Dilated (Congestive) CMP** Characterized by progressive cardiac failure and dilation of all four chambers. Possible associations include viral myocarditis, toxic damage (e.g. cobalt, chemotherapy), genetic mutations, chronic alcoholism, and peripartum.
- **Arrhythmogenic CMP** Ventricular arrhythmias, typically in young individuals, with family history and genetic mutations in desmosome proteins. Characterized by fibrofatty replacement of ventricular myocardium.
- **Hypertrophic CMP** Asymmetrical hypertrophy affecting the interventricular septum, often with genetic mutations in sarcomere proteins. Can cause dyspnea, angina, heart failure, and sudden death.
- **Restrictive (Obliterative or infiltrative) CMP** Restriction in ventricular filling due to conditions like cardiac amyloidosis, endocardial fibroelastosis, endomyocardial fibrosis, and carcinoid heart disease.

Morphologic Changes and Clinical Effects of CMP

- **Dilated CMP** Enlarged heart with prominent dilatation of all chambers, thickened endocardium, and possible mural thrombi. Microscopy shows hypertrophy, atrophy, fibrosis, and inflammatory cell infiltrate. Clinically, progressive heart failure, arrhythmias, and reduced life expectancy (average survival of less than 5 years).
- **Arrhythmogenic CMP** Enlarged heart with fibrofatty replacement of ventricular myocardium, more often affecting the right side. Microscopy, possible mild inflammation and myocyte necrosis. Clinically, high risk of sudden cardiac arrest and sudden death due to ventricular arrhythmias.
- **Hypertrophic CMP** Cardiac enlargement with asymmetrical myocardial hypertrophy, particularly of the interventricular septum. Microscopy shows disorganization of myocardial fibers, nuclear enlargement, and interstitial fibrosis. Clinically, often asymptomatic, but can cause dyspnea, angina, heart failure, and sudden death, especially with heavy physical activity.
- **Restrictive CMP** Thickened endocardium and diminished chamber volume; cardiac amyloidosis shows subendocardial deposits; endocardial fibroelastosis shows proliferation of collagen and elastic tissue. Clinically, restriction in ventricular filling leads to heart failure, with specific effects depending on underlying causes like amyloidosis or fibroelastosis.

PERICARDIAL DISEASES

Diseases of the pericardium are usually secondary to, or associated with, other cardiac and systemic diseases. These are discussed under two headings:

- I. Pericardial accumulations
- II. Pericardial inflammation (pericarditis)

PERICARDIAL ACCUMULATIONS

Accumulation of fluid in the pericardial sac may be watery or pure blood.

Accordingly, it is of 2 types: hydropericardium (accumulation of effusion fluid) and hemopericardium (accumulation of blood).

A. HYDROPERICARDIUM (PERICARDIAL EFFUSION)

Accumulation of fluid in the pericardial cavity due to noninflammatory causes is called hydropericardium or pericardial effusion. Normally, the pericardial cavities contain 30–50 mL of clear watery fluid. Considerable quantities of fluid (up to 1,000 mL) can be accommodated in the pericardial cavity without seriously affecting the cardiac function if the accumulation is slow. But *sudden accumulation* of a smaller volume (up to 250 mL) may produce deficient diastolic filling of the cardiac chambers (cardiac tamponade). Pericardial effusion is detected by cardiac enlargement in the X-rays and by faint apex beat.

The various types of effusions and their causes are as follows:

1. Serous effusions This is the most common type occurring in conditions in which there is generalized edema, e.g. in cardiac (in CHF), renal, nutritional and hepatic causes. It may also occur due to hypothyroidism. The serous effusion is clear, watery, straw-colored with specific gravity less than 1.015 (transudate). The serosal surface is smooth and glistening.

2. Serosanguineous effusion This type is found following blunt trauma to chest and cardiopulmonary resuscitation.

3. Chylous effusion Milky or chylous fluid accumulates in conditions causing lymphatic obstruction.

B. HEMOPERICARDIUM Accumulation of *pure blood* in the pericardial sac is termed hemopericardium. The condition must be distinguished from hemorrhagic pericarditis where small quantities of blood can be mixed with inflammatory exudate into the pericardial cavity. Massive and sudden bleeding into the sac causes compression of the heart leading to cardiac tamponade. The causes of hemopericardium are as under:

- i) Rupture of the heart through a myocardial infarct
- ii) Rupture of dissecting aneurysm
- iii) Bleeding diathesis such as in scurvy, acute leukemia, thrombocytopenia
- iv) Trauma following cardiopulmonary resuscitation or by laceration of a coronary artery

PERICARDITIS

Pericarditis is the inflammation of the pericardial layers and is generally secondary to diseases in the heart or caused by systemic diseases. Primary or idiopathic pericarditis is quite rare. Based on morphologic appearance, pericarditis is classified into acute and chronic types, each of which may have several etiologies. Acute and chronic pericarditis has further subtypes based on the character of the exudate (Table 17.11).

TABLE 17.11 Classification of pericarditis.

A. ACUTE PERICARDITIS	
	1. Serous pericarditis
	2. Fibrinous or serofibrinous pericarditis
	3. Purulent or fibrinopurulent pericarditis
	4. Hemorrhagic pericarditis
B. CHRONIC PERICARDITIS	
	1. Tuberculous pericarditis
	2. Chronic adhesive pericarditis
	3. Chronic constrictive pericarditis
	4. Pericardial plaques (milk spots, soldiers' spots)

A. ACUTE PERICARDITIS

Acute bacterial and non-bacterial pericarditis is the most frequently encountered form of pericarditis. These may have the following subtypes:

1. SEROUS PERICARDITIS Acute pericarditis may be accompanied by accumulation of serous effusion which differs from transudate of hydropericardium in having increased protein content and higher specific gravity. Its various causes are as under:

- i) Viral infection, e.g. coxsackie A or B viruses, influenza virus, mumps virus, adenovirus and infectious mononucleosis.
- ii) Rheumatic fever.
- iii) Rheumatoid arthritis.
- iv) Systemic lupus erythematosus.
- v) Involvement of the pericardium by malignant tumor in the vicinity, e.g. carcinoma lung, mesothelioma and mediastinal tumors.
- vi) Tuberculous pericarditis in the early stage.

The fluid accumulation is generally not much and ranges from 50 to 200 mL but may sometimes be large enough to cause cardiac tamponade.

Microscopically, the epicardial and pericardial surfaces show infiltration by some neutrophils, lymphocytes and histiocytes. The fluid usually resorbs with the resolution of underlying disease.

2. FIBRINOUS AND SEROFIBRINOUS PERICARDITIS The response of the pericardium by fibrinous exudate is the most common type of pericarditis. Quite often, there is admixture of fibrinous exudate with serous fluid. The various causes of this type of pericarditis are as follows:

- i) Uremia
- ii) Myocardial infarction
- iii) Rheumatic fever
- iv) Trauma such as cardiac surgery
- v) Acute bacterial infections

The amount of fluid accumulation is variable. The cardiac surface is characteristically covered by dry or moist, shaggy, fibrinous exudate which gives '*bread and butter*' appearance. Clinically, these cases manifest by friction rub. In less extensive cases of fibrinous or serofibrinous pericarditis, there is complete resorption of the exudate. In cases with advanced fibrinous exudate, pericarditis heals by organization and develops fibrous adhesions resulting in adhesive pericarditis.

3. PURULENT OR FIBRINOPURULENT PERICARDITIS

Purulent or fibrinopurulent pericarditis is mainly caused by pyogenic bacteria (e.g. staphylococci, streptococci and pneumococci) and less frequently by fungi and parasites. The infection may spread to the pericardium by the following routes:

- i) By direct extension from neighboring inflammation, e.g. in empyema of the pleural cavity, lobar pneumonia, infective endocarditis and mediastinal infections
- ii) By hematogenous spread
- iii) By lymphatic permeation
- iv) Direct implantation during cardiac surgery

Generally, fibrinous or serofibrinous pericarditis precedes the development of purulent pericarditis. The amount of

exudate is variable and is generally thick, creamy pus, coating the pericardial surfaces.

Microscopically, besides the purulent exudate on the pericardial surfaces, the serosal layers show dense infiltration by neutrophils (**Fig. 17.46**). Purulent exudate generally does not resolve completely but instead heals by organization resulting in adhesive or chronic constrictive pericarditis.

4. HEMORRHAGIC PERICARDITIS Hemorrhagic pericarditis is the one in which the exudate consists of admixture of an inflammatory effusion of one of the foregoing types along with blood. The causes are as under:

- i) Neoplastic involvement of the pericardium
- ii) Hemorrhagic diathesis with effusion
- iii) Tuberculosis
- iv) Severe acute infections
- v) Uremia

The outcome of hemorrhagic pericarditis is generally similar to that of purulent pericarditis.

B. CHRONIC PERICARDITIS

Chronic pericarditis is the term used for tuberculous pericarditis and the healed stage of one of the various forms of acute pericarditis already described. It includes tuberculous pericarditis, chronic adhesive pericarditis, chronic constrictive pericarditis, and the pericardial plaques.

1. TUBERCULOUS PERICARDITIS Tuberculous pericarditis is the most frequent form of granulomatous inflammation of the pericardium. The lesions may occur by one of the following mechanisms:

- i) Direct extension from an adjacent focus of tuberculosis.
- ii) By lymphatic spread, e.g. from tracheobronchial lymph nodes, chronic pulmonary tuberculosis or infected pleura.

The exudate is slightly turbid, caseous or blood-stained with sufficient fibrin. Tubercles are generally visible on the pericardial surfaces and sometimes caseous areas are also visible to the naked eye.

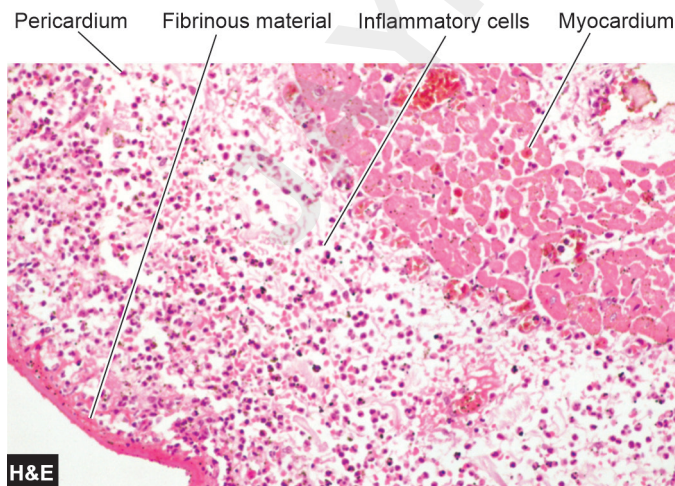


Figure 17.46 Fibrinopurulent pericarditis. The pericardium is covered with pink serofibrinous exudates. The space between the layers of the pericardium contains numerous mixed inflammatory cells which are seen to extend into underlying myocardium.

Microscopically, typical tuberculous granulomas with caseation necrosis are seen in the pericardial wall. The lesions generally do not resolve but heal by fibrosis and calcification resulting in chronic constrictive pericarditis.

2. CHRONIC ADHESIVE PERICARDITIS Chronic adhesive pericarditis is the stage of organization and healing by formation of fibrous adhesions in the pericardium following preceding fibrinous, suppurative or hemorrhagic pericarditis. The process begins with the formation of granulation tissue and neovascularization. Subsequently, fibrous adhesions develop between the parietal and the visceral layers of the pericardium and obliterate the pericardial space (**Fig. 17.47, A**). Sometimes, fibrous adhesions develop between the parietal pericardium and the adjacent mediastinum and are termed *adhesive mediastinopericarditis*. Chronic adhesive pericarditis differs from chronic constrictive pericarditis in that the former does not compromise the function of the heart. However, cardiac hypertrophy and dilatation may occur in severe cases of adhesive pericarditis due to increased workload.

3. CHRONIC CONSTRICTIVE PERICARDITIS This is a rare condition characterized by dense fibrous or fibrocalcific thickening of the pericardium resulting in mechanical interference with the function of the heart and reduced cardiac output. The condition usually results from long-standing preceding causes, e.g.

- i) Tuberculous pericarditis
- ii) Purulent pericarditis
- iii) Hemopericardium
- iv) Concato disease (polyserositis), i.e. serositis and accumulation of effusion fluid in multiple serous cavities, infective or autoimmune in origin
- v) Rarely, acute non-specific and viral pericarditis

The heart is encased in 0.5 to 1 cm thick, collagenized pericardium, that is often calcified. As a result, the heart fails to dilate during diastole. The dense fibrocollagenous tissue may cause narrowing of the openings of the vena cavae, resulting in obstruction to the venous return to the right heart and consequent right heart failure. In contrast to chronic adhesive pericarditis, hypertrophy and dilatation do not occur due to dense fibrous scarring; instead, the heart size is normal or smaller (**Fig. 17.47, B**).

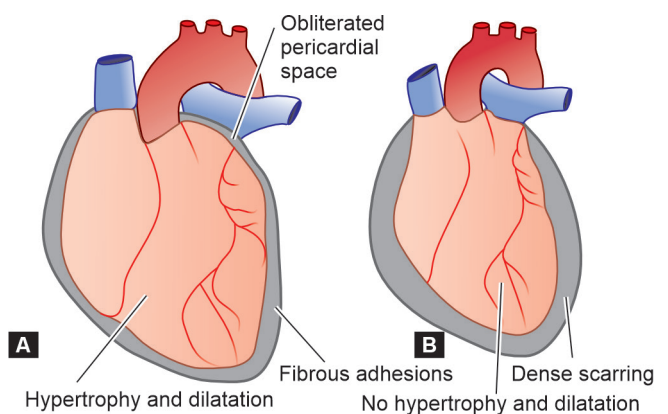


Figure 17.47 Appearance of the heart and the pericardium in chronic adhesive (A) and chronic constrictive pericarditis (B).

SUMMARY Pericardial Diseases**Pericardial Effusion and its Types**

Accumulation of fluid in the pericardial sac. Two types:

- *Hydropericardium* Watery collection (serous, serosanguinous, chylous).
- *Hemopericardium* Collection of pure blood.

Pericarditis and its Types

Inflammation of the pericardial layers may be acute or chronic.

- *Acute pericarditis* Its types:
 - ◆ Serous: yellowish translucent fluid accumulation
 - ◆ Fibrinous: fibrinous fluid accumulation (chance of organization and adhesion >serous)
 - ◆ Purulent: fibrino-purulent fluid accumulation (chance of organization and adhesion >>serous and >fibrinous)
 - ◆ Hemorrhagic: accumulation of scant blood with inflammatory exudate (not pure blood, like in hemopericardium) (chance of organization and adhesion >> serous and >fibrinous)
- *Chronic pericarditis* Its types: chronic adhesive, chronic constrictive and tubercular pericarditis

TUMORS OF THE HEART

Tumors of the heart are classified into primary and secondary, the latter being more common than the former.

PRIMARY TUMORS

Primary tumors of the heart are quite rare, found in 0.04% of autopsies. In decreasing order of frequency, the benign tumors seen in the heart are myxoma, lipoma, fibroelastoma, rhabdomyoma, hemangioma and lymphangioma. The malignant tumors are still rarer, the important ones are rhabdomyosarcoma, angiosarcoma and malignant mesothelioma. Out of all these, only myxoma of the heart requires elaboration.

MYXOMA This is the most common primary tumor of the heart comprising about 50% of all primary cardiac tumors. Majority of them occur in the age range of 30 to 60 years. Myxomas are seen in any cardiac chamber or the valves, but 90% of them are situated in the left atrium.

Grossly, myxomas are mostly single but can be multiple. They range in size from less than 1 to 10 cm, polypoid, pedunculated, spherical, soft and hemorrhagic masses resembling an organizing mural thrombus (**Fig. 17.48, A**). Some investigators consider myxoma to be organizing mural thrombus rather than a true neoplasm.

Microscopically, the tumor shows the following features (**Figs. 17.48, B, C**):

- i) There is abundant myxoid or mucoid intercellular stroma positive for mucin.
- ii) The cellularity is sparse. The tumor cells are generally stellate-shaped, spindle and polyhedral, scattered in the stroma. Occasional multinucleate tumor giant cells are present.
- iii) Numerous capillary-sized blood vessels are found, and the tumor cells may be aggregated around them.
- iv) A few lymphocytes, plasma cells and macrophages are seen.
- v) Foci of hemorrhage and deposits of hemosiderin granules are often present.

SECONDARY TUMORS

Metastatic tumors of the heart are more common than the primary tumors. About 10% of cases of disseminated cancer may metastasize in the heart. Most of them result from hematogenous or lymphatic spread. In descending order of frequency, primary sites of origin are carcinoma of the lung, breast, malignant lymphoma, leukemia and malignant melanoma. Occasionally, there may be direct extension of a primary intrathoracic tumor such as carcinoma of the lung into the pericardium and into the cardiac chambers.

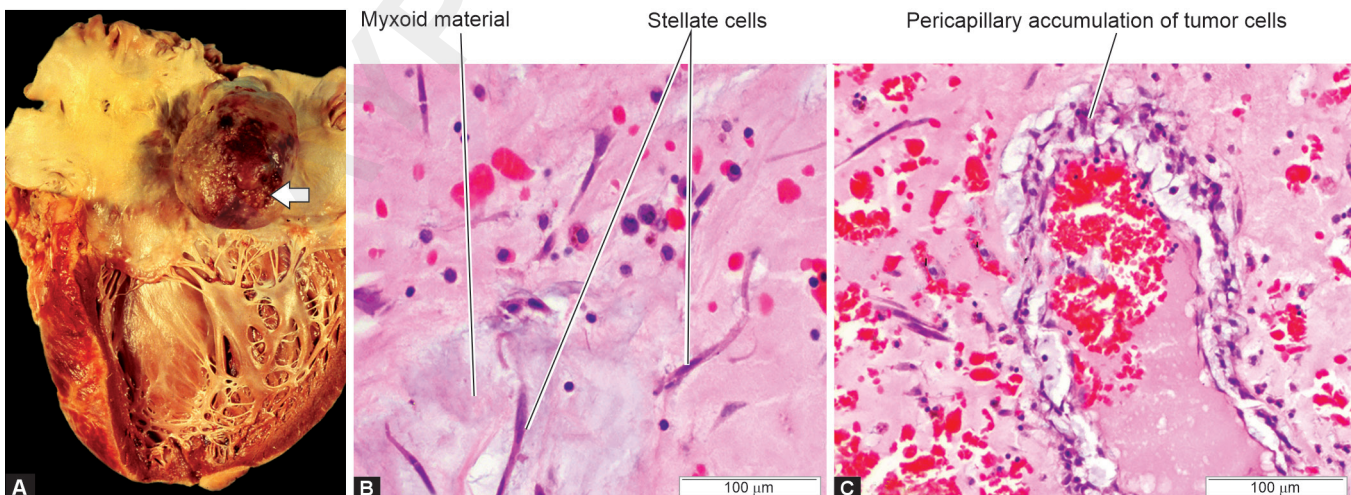


Figure 17.48 Atrial myxoma. A, Left atrium contains dark blood clot-like spherical tan mass (arrow). B, Microscopy shows a benign tumor composed of stellate cells and myxoid stroma (arrows). C, It shows tumor cell condensation around small capillaries within the tumor (arrow). (A, Courtesy of Dr Ivan Damjanov, Department of Pathology and Laboratory Medicine, The University of Kansas School of Medicine, Kansas, USA.) (Images B, C, contributed by Dr Sudheer Arava, Professor of Pathology, AIIMS, New Delhi).

SUMMARY Tumors of the Heart**Primary Tumors**

- Rare, found in 0.04% of autopsies.
- Benign tumors: Myxoma, lipoma, fibroelastoma, rhabdomyoma, hemangioma, lymphangioma.
- Malignant tumors: Rhabdomyosarcoma, angiosarcoma, malignant mesothelioma.

Myxoma

- Most common primary tumor, about 50% of all primary cardiac tumors.
- Common site: 90% occur in the left atrium.
- Appearance: Single or multiple, polypoid, pedunculated, soft, hemorrhagic masses.
- Morphology: Myxoid stroma, sparse cellularity with stellate-shaped, spindle, and polyhedral cells, abundant capillary-sized blood vessels.

Secondary Tumors

- More common than primary tumors.
- About 10% of disseminated cancers metastasize to the heart.
- Common primary sites: Lung, breast, malignant lymphoma, leukemia, malignant melanoma.

PATHOLOGY OF CARDIOVASCULAR INTERVENTIONS

With the development of surgical and non-surgical coronary revascularization procedures in coronary artery disease (CAD), it has become possible to study the pathology of native as well as grafted vessels. Besides, the myocardial tissue by endomyocardial biopsy is also accessible for histopathologic study.

ENDOMYOCARDIAL BIOPSY

Endomyocardial biopsy (EMB) is done for making a final histopathologic diagnosis in certain cardiac diseases, where the other diagnostic modalities have not yield results. The main *indications* for EMB are myocarditis, cardiac transplant cases, restrictive heart disease, infiltrative heart diseases such as amyloidosis, storage disorders, etc.

EMB is done by biopsy forceps introduced via cardiac catheter into either of the ventricles, but preferably the right

ventricle is biopsied for its relative ease and safety. The route for the catheter may be through internal jugular vein or femoral vein for accessing the right ventricle.

CORONARY ARTERY BYPASS GRAFTING

Coronary artery bypass grafting (CABG) employs the use of autologous grafts to replace or bypass the blocked coronary arteries. Most frequently used is autologous graft of saphenous vein which is reversed (due to valves in the vein) and transplanted; alternatively, left internal mammary artery may be used which is available nearest to the operative area of the heart. The long-term follow-up of CABG surgery has yielded the following observations on morphology of grafted vessel:

1. In a reversed saphenous vein graft, long-term luminal patency is 50% after 10 years. Morphologic changes which develop in grafted veins include thrombosis in early stage, intimal thickening and graft atherosclerosis with or without complicated lesions.
2. Internal mammary artery graft, however, has a patency of more than 90% after 10 years.
3. Atherosclerosis with superimposed complications may develop in native coronary artery distal to the grafted vessel as well as in the grafted vessel.

SUMMARY Pathology of Cardiovascular Interventions**Endomyocardial Biopsy (EMB)**

- Primarily performed on the right ventricle for histopathologic diagnosis of myocarditis, cardiac transplant rejection, restrictive heart diseases, and infiltrative heart diseases (e.g. amyloidosis).

Coronary Artery Bypass Grafting (CABG)

- Uses autologous saphenous vein grafts or internal mammary artery grafts to bypass blocked coronary arteries.
 - ◆ *Saphenous vein graft* 50% luminal patency after 10 years; prone to thrombosis, intimal thickening, and graft atherosclerosis.
 - ◆ *Internal mammary artery graft* Over 90% luminal patency after 10 years; higher long-term success rate compared to saphenous vein grafts.
 - ◆ *Post-CABG atherosclerosis* Can develop in native coronary arteries distal to graft and within the graft itself.



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