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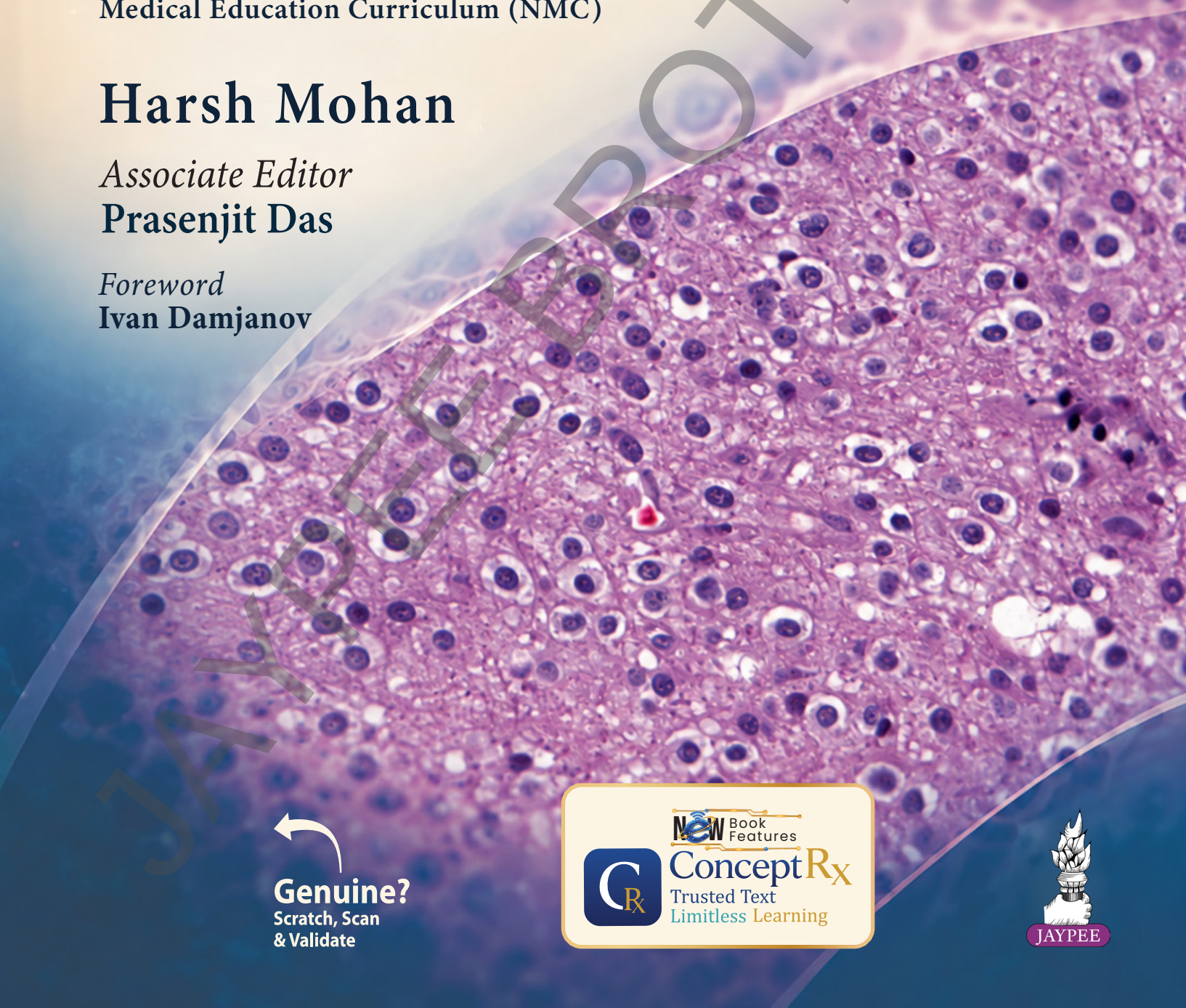
TEXTBOOK OF PATHOLOGY

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

Harsh Mohan

Associate Editor
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Foreword
Ivan Damjanov



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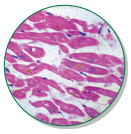
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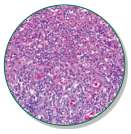
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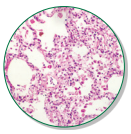


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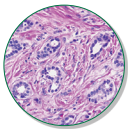
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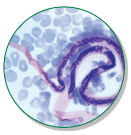
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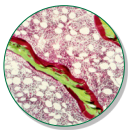
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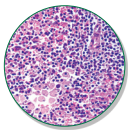
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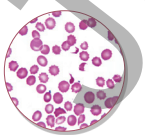
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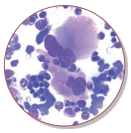


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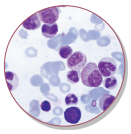
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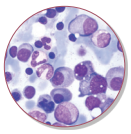
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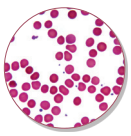
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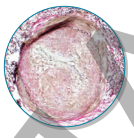
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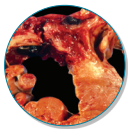
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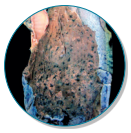
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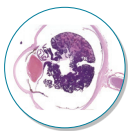
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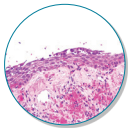
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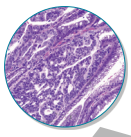
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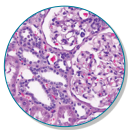
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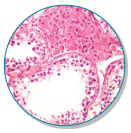
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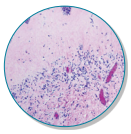
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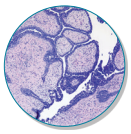
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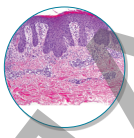
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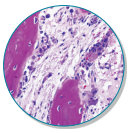
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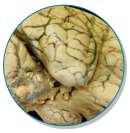
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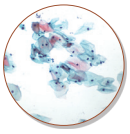
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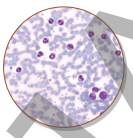
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Chapter 17 The Heart

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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

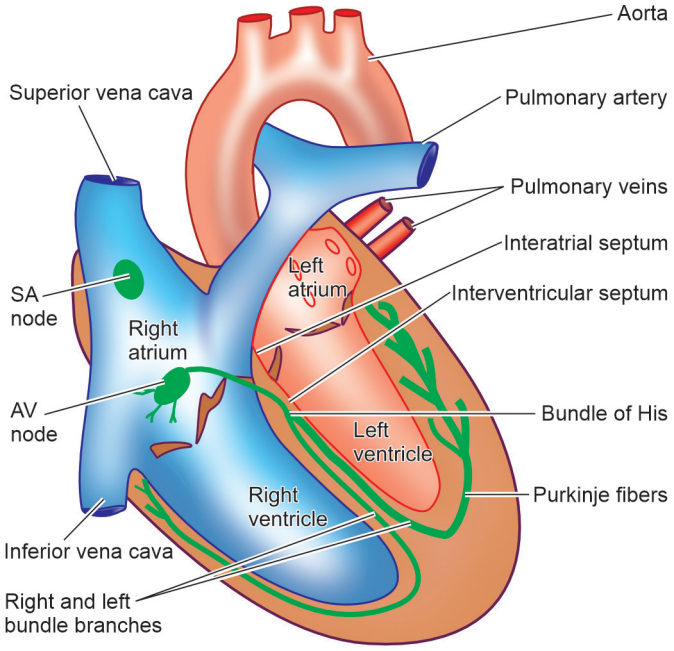


Figure 17.1 The normal anatomic structure of the heart. (SA, sinoatrial; AV, atrioventricular).

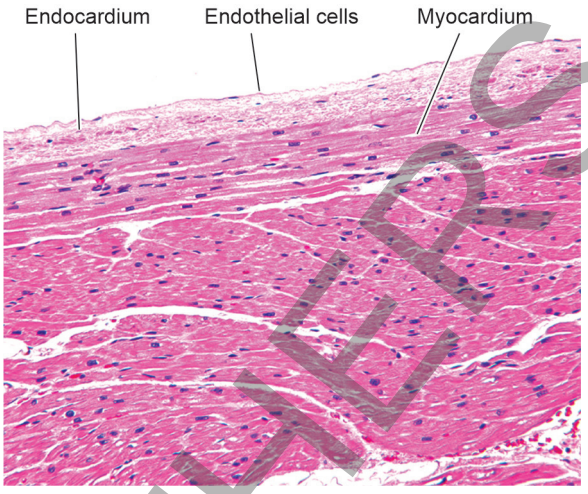


Figure 17.2 Normal microscopic structure of the heart. The endocardium is a thin layer composed of loose connective tissue. The myocardium is composed of striated muscle cells, arranged in syncytium. (Reproduced with permission from *Atlas of Histopathology* by Ivan Damjanov 2012, Jaypee Brothers Medical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

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.

- 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

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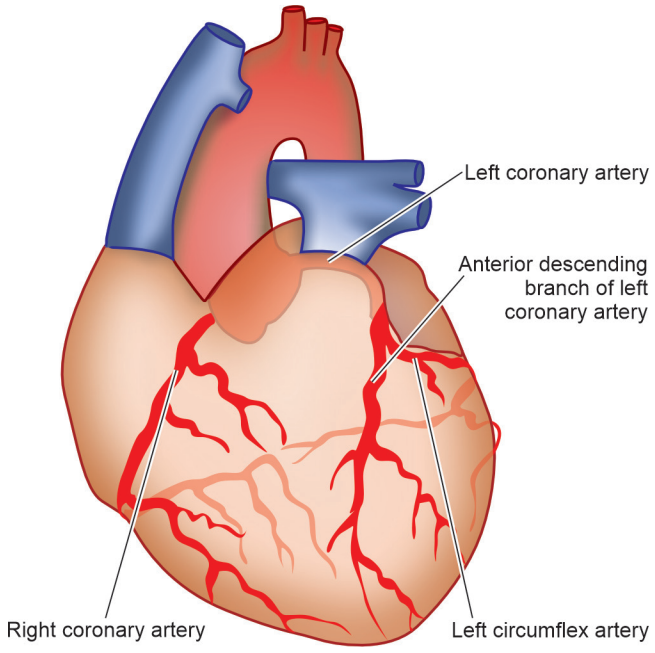


Figure 17.3 Distribution of blood supply to the heart.

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:

i) Ischemic heart disease
ii) Myocarditis
iii) Cardiomyopathies
iv) Metabolic disorders, e.g. beriberi
v) 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.

i) **Increased pressure load** may occur in the following states:

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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)**:

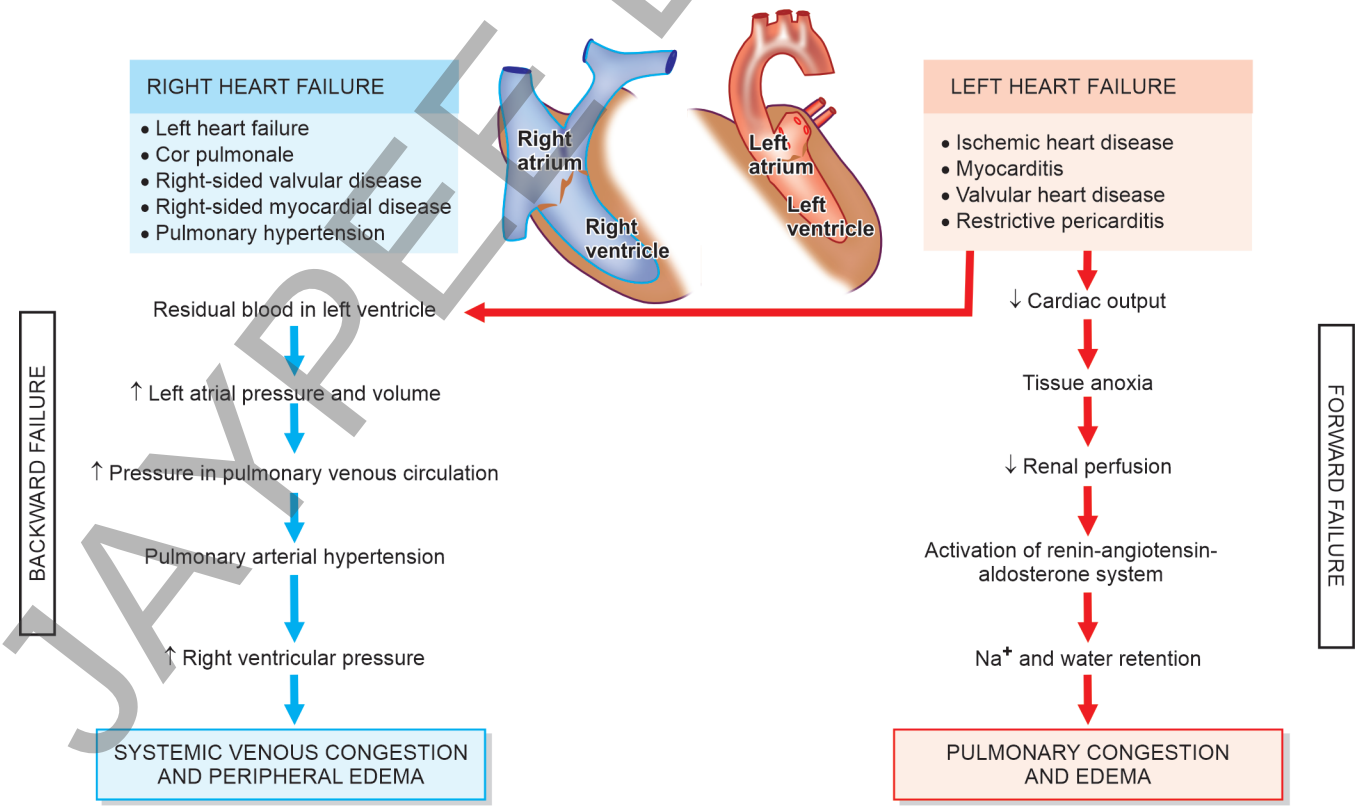


Figure 17.4 Schematic evolution of congestive heart failure and its effects.

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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**.

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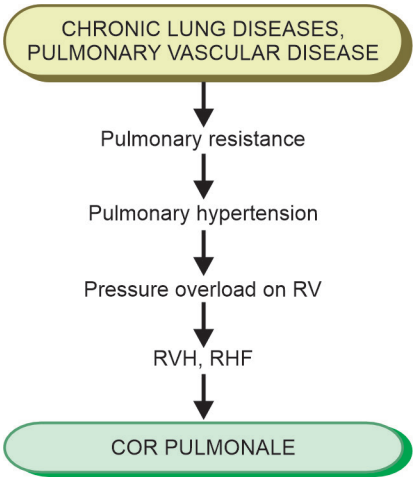


Figure 17.5 Pathogenesis of cor pulmonale. (RV, right ventricle; RVH, right ventricular hypertrophy, RHF, right heart failure).

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:

i) Systemic hypertension, most common
ii) Aortic stenosis and insufficiency
iii) Mitral insufficiency
iv) Coarctation of the aorta
v) Occlusive coronary artery disease
vi) Congenital anomalies like septal defects and patent ductus arteriosus
vii) 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:

i) Cor pulmonale from chronic lung diseases (e.g. chronic emphysema, bronchiectasis, pneumoconiosis, pulmonary vascular disease, etc.), most common
ii) Pulmonary stenosis and insufficiency
iii) Tricuspid insufficiency
iv) Mitral stenosis and/or insufficiency
v) 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.

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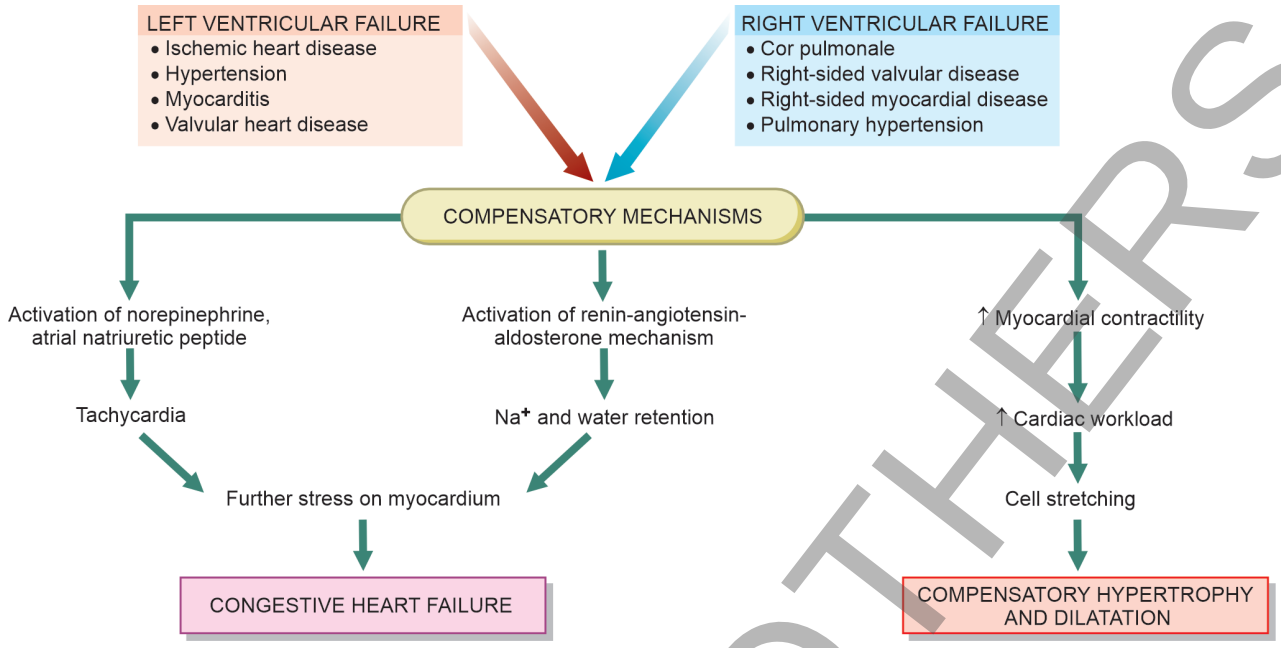


Figure 17.6 Schematic pathophysiology of compensatory mechanisms in cardiac failure.

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:

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

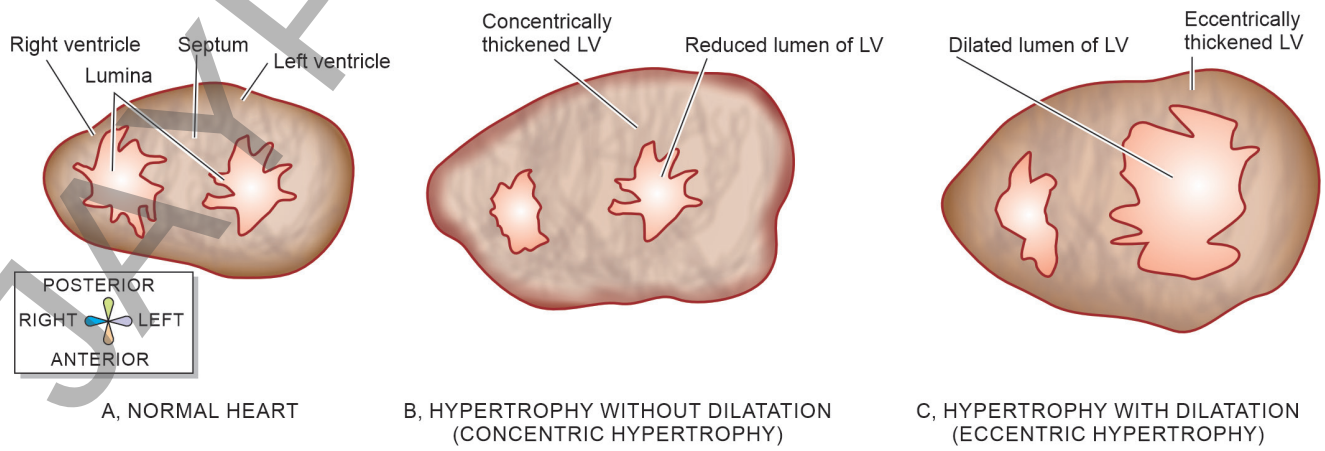


Figure 17.7 Schematic diagram showing transverse section through the ventricles with left ventricular hypertrophy (concentric and eccentric). (LV, left ventricle).

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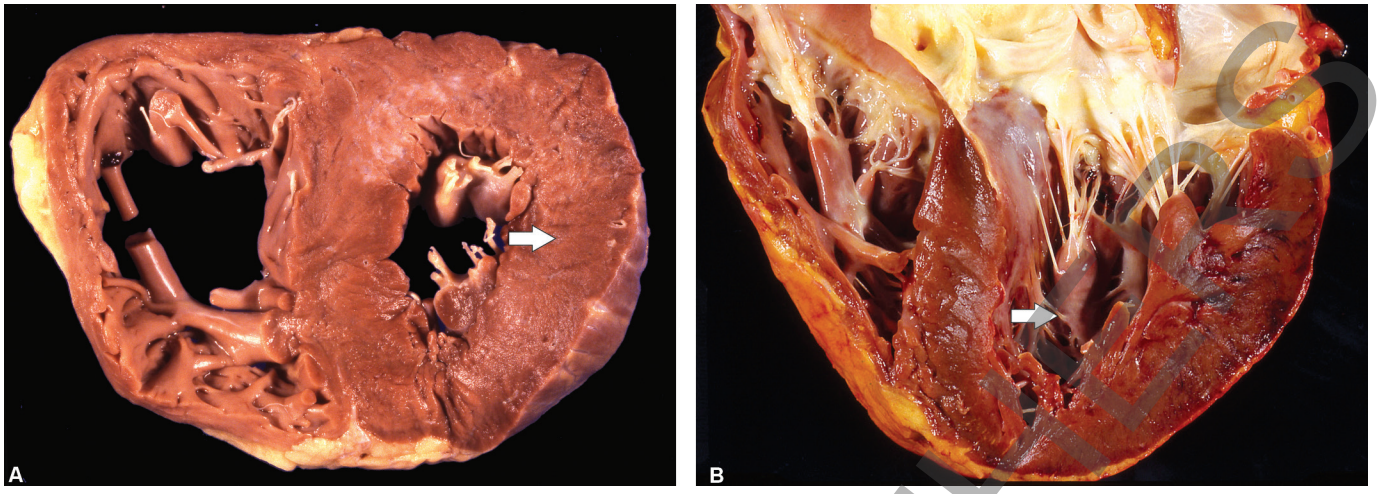


Figure 17.8 A, *Concentric cardiac hypertrophy*. Weight of the heart in this hypertensive deceased is increased. The opened-up chambers show concentric thickening of left ventricular wall (white arrow) with obliterated lumen (hypertrophy without dilatation). B, *Eccentric cardiac hypertrophy*. The heart 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.

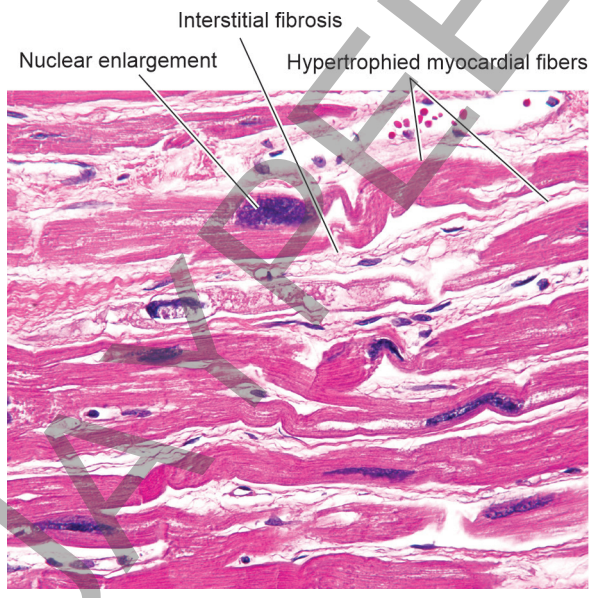


Figure 17.9 Cardiac hypertrophy. Longitudinally sectioned cardiac myocytes are thick with enlarged, hyperchromatic vesicular nuclei and abundant cytoplasm. (Reproduced with permission from *Atlas of Histopathology* by Ivan Damjanov 2012, Jaypee Brothers Medical Publishers Pvt Ltd, New Delhi).

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 dilation) 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

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- *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. Left-to-right shunts (Acyanotic or late cyanotic group) 1. Ventricular septal defect (VSD), *most common* 2. Atrial septal defect (ASD) 3. Patent ductus arteriosus (PDA) *B. Right-to-left shunts (Cyanotic group)* 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.

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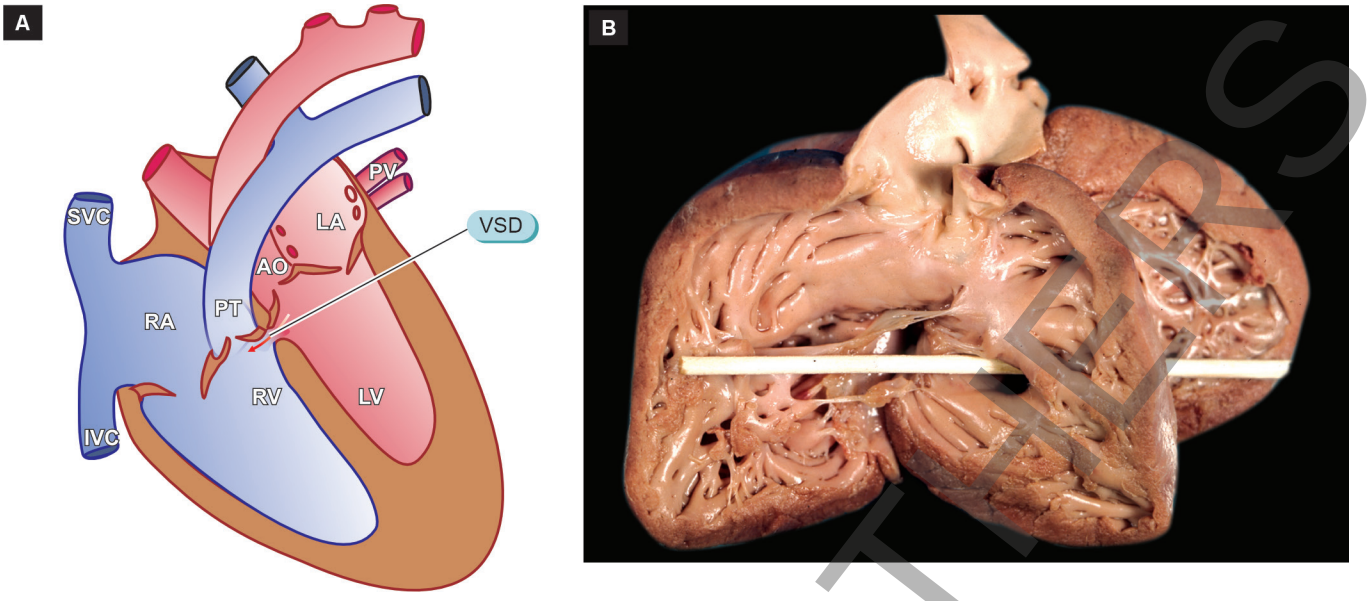


Figure 17.10 Ventricular septal defect. A, Schematic representation. B, The opened up chambers of the heart show a communication in the interventricular septum superiorly (white pipe). (LA, left atrium; LV, left ventricle; AO, aorta; PV, pulmonary valve; PT, pulmonary trunk; RA, right atrium; RV, right 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.

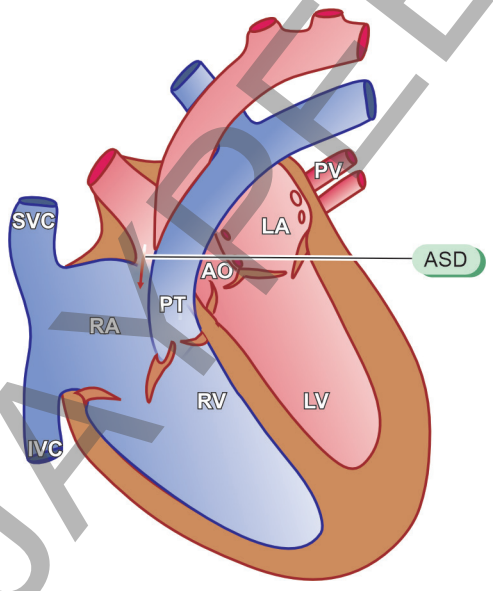


Figure 17.11 Atrial septal defect fossa ovalis type, a schematic representation. (LA, left atrium; LV, left ventricle; PV, pulmonary vein; AO, aorta; PT, pulmonary trunk; RA, right atrium; RV, right ventricle; SVC, superior vena cava; IVC, inferior vena cava; ASD, atrial septal defect).

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 in infants 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.

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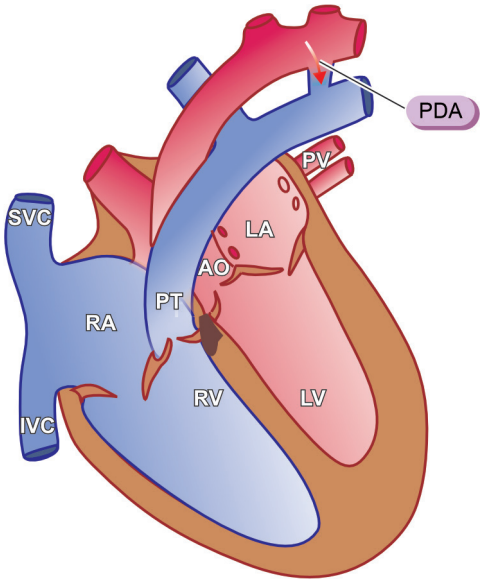


Figure 17.12 Patent ductus arteriosus, a schematic representation. (LA, left atrium; LV, left ventricle; PT, pulmonary trunk; PV, pulmonary vein, AO, aorta; RA, right atrium; RV, right ventricle; SVC, superior vena cava; IVC, inferior vena cava; PDS, patent ductus arteriosus).

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

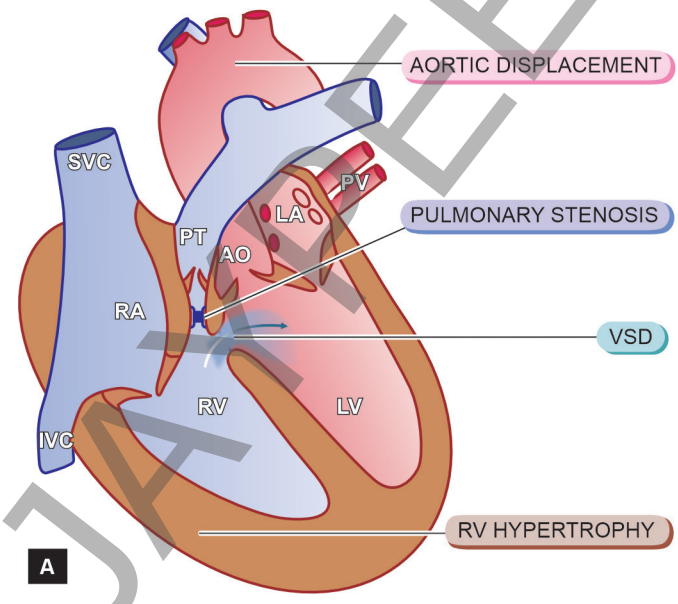




Figure 17.13 Tetralogy of Fallot, A, a schematic representation. (LA, left atrium; LV, left ventricle; PT, pulmonary trunk; PV, pulmonary vein; AO, aorta; RA, right atrium; RV, right ventricle; SVC, superior vena cava; IVC, inferior vena cava; PDA, patent ductus arteriosus; VSD, ventricular septal defect). 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* = *P*ulmonary stenosis, *R*ight ventricular hypertrophy, *O*verriding of aorta, *V*entricular septal defect.

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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.

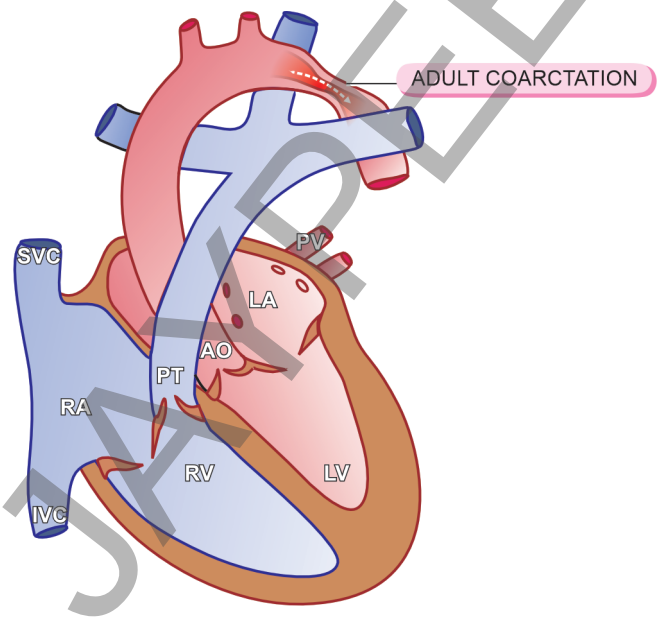


Figure 17.14 Postductal or adult type coarctation of the aorta, a schematic representation. (LA, left atrium; LV, left ventricle; PT, pulmonary trunk; PV, pulmonary vein; AO, aorta; RA, right atrium; RV, right ventricle; SVC, superior vena cava; IVC, inferior vena cava).

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

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) Supravalvular 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.

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.

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- *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

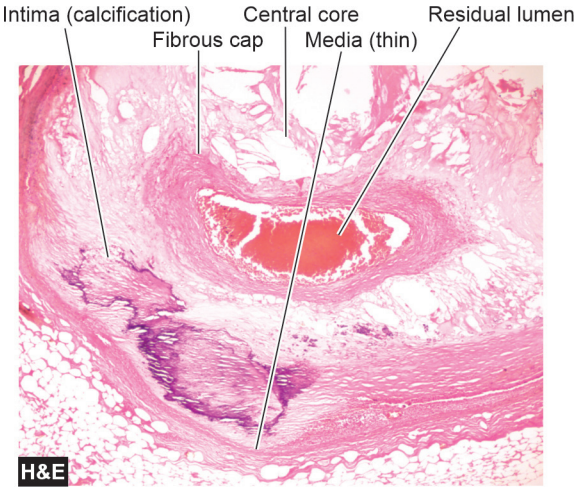


Figure 17.15 Left anterior descending (LAD) coronary artery showing critical narrowing with eccentric luminal obliteration due to atheromatous plaque having a hard sclerotic and calcified core. The residual lumen is reduced to a slit-like.

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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.

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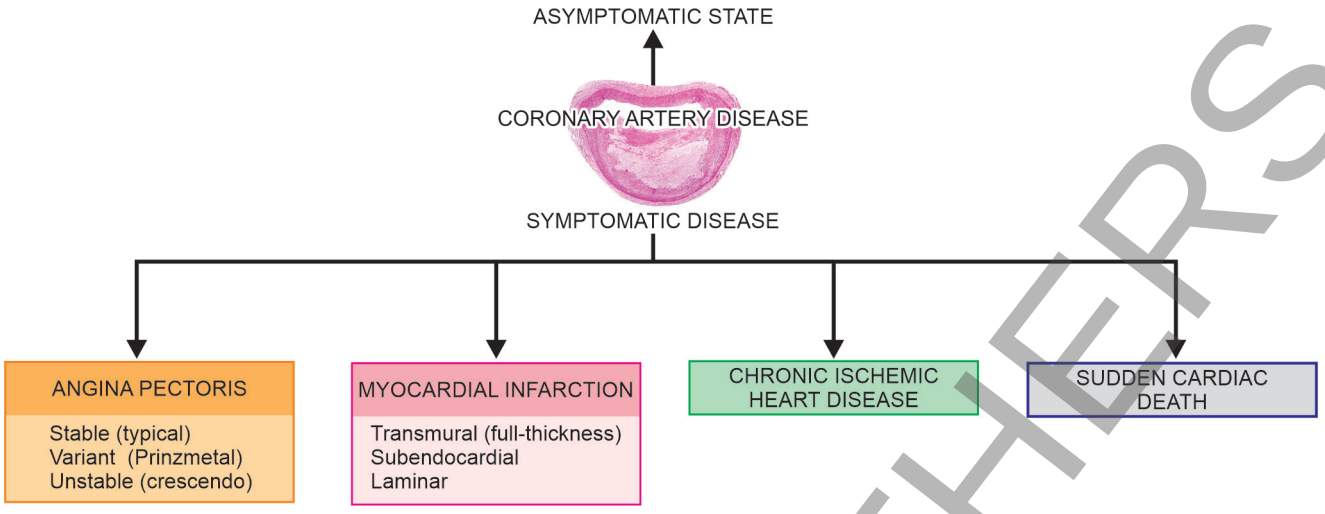


Figure 17.16 Spectrum of coronary ischemic manifestations.

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:

i) Reduced coronary blood flow, e.g. in coronary artery disease or shock.

ii) Increased myocardial demand, e.g. during exercise or emotional stress.

iii) 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 sever 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:

i) *Superimposed coronary thrombosis* due to disruption of plaque is seen in about half the cases of AMI. Infusion of intracoronary fibrinolysins 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.

ii) *Intramural hemorrhage* is found in about one-third cases of AMI.

Plaque hemorrhage and thrombosis may occur together in some cases.

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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

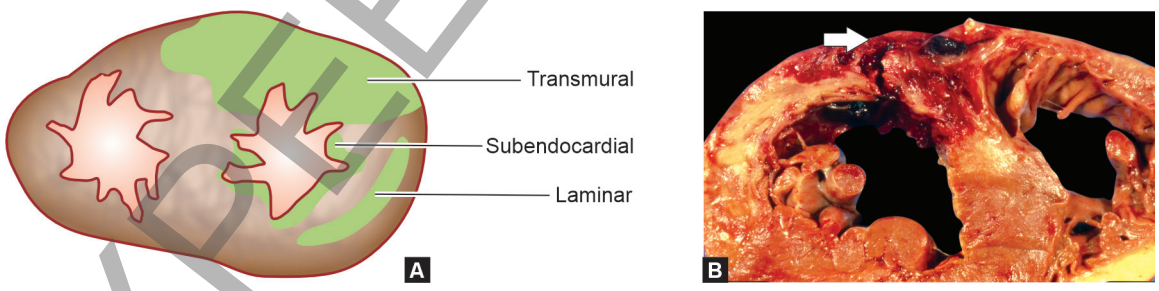


Figure 17.17 A, Diagrammatic representation of extent of myocardial infarction in the depth of myocardium. B, Cross section of the heart having transmural infarct of left ventricle showing ruptured ventricular wall (arrow). (Gross image courtesy by Dr Ivan Damjanov, Department of Pathology and Laboratory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

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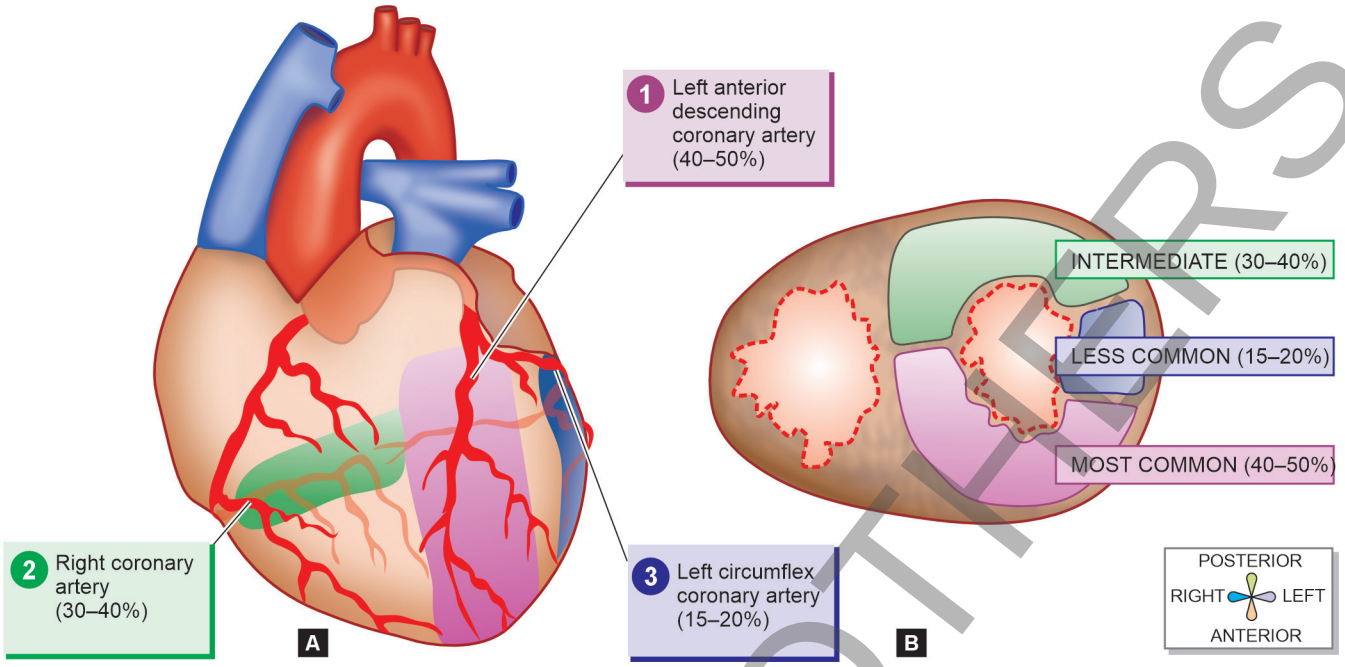


Figure 17.18 Common locations and the regions of involvement in myocardial infarction. The figure shows region of myocardium affected by stenosis of three respective coronary trunks in descending order shown as: 1) left anterior descending coronary, 2) right coronary and 3) left circumflex coronary artery. 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).

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