Heart Failure

The abnormalities described above often culminate in heart failure, an extremely common result of many forms of heart disease. In heart failure, often called congestive heart failure (CHF), the heart is unable to pump blood at a rate commensurate with the requirements of the metabolizing tissues or can do so only at an elevated filling pressure. Although usually caused by a slowly developing intrinsic deficit in myocardial contraction, a similar clinical syndrome is present in some patients with heart failure caused by conditions in which the normal heart is suddenly presented with a load that exceeds its capacity (e.g., fluid overload, acute myocardial infarction, acute valvular dysfunction) or in which ventricular filling is impaired (see below). CHF is a common and often recurrent condition with a poor prognosis. The magnitude of the problem is exemplified by the impact of CHF in the United States, where each year it affects nearly 5 million individuals, is the underlying or contributing cause of death of an estimated 300,000, and necessitates over 1 million hospitalizations. Moreover, CHF is the leading discharge diagnosis in hospitalized patients over age 65 and has an associated annual cost of $18 billion. In many pathologic states, the onset of heart failure is preceded by cardiac hypertrophy, the compensatory response of the myocardium to increased mechanical work (see below).

The cardiovascular system maintains arterial pressure and perfusion of vital organs in the presence of excessive hemodynamic burden or disturbance in myocardial contractility by a number of mechanisms. The most important are:

- The Frank-Starling mechanism, in which the increased preload of dilation (thereby increasing cross-bridges within the sarcomeres) helps to sustain cardiac performance by enhancing contractility
- Myocardial structural changes, including augmented muscle mass (hypertrophy) with or without cardiac chamber dilation, in which the mass of contractile tissue is augmented
- Activation of neurohumoral systems, especially (1) release of the neurotransmitter norepinephrine by adrenergic cardiac nerves (which increases heart rate and augments myocardial contractility and vascular resistance), (2) activation of the renin-angiotensin-aldosterone system, and (3) release of atrial natriuretic peptide.

These adaptive mechanisms may be adequate to maintain the overall pumping performance of the heart at relatively normal levels, but their capacity to sustain cardiac performance may ultimately be exceeded. Moreover, pathologic changes, such as apoptosis, cytoskeletal alterations, and extracellular matrix (particularly collagen) synthesis and remodeling, may also occur, causing structural and functional disturbances. Most instances of heart failure are the consequence of progressive deterioration of myocardial contractile function (systolic dysfunction), as often occurs with ischemic injury, pressure or volume overload, or dilated cardiomyopathy. The most frequent specific causes are ischemic heart disease and hypertension. Sometimes, however, failure results from an inability of the heart chamber to relax, expand, and fill sufficiently during diastole to accommodate an adequate ventricular blood volume (diastolic dysfunction), as can occur with massive left ventricular hypertrophy, myocardial fibrosis, deposition of amyloid, or constrictive
pericarditis. \[12\] Whatever its basis, CHF is characterized by diminished cardiac output (sometimes called forward failure) or damming back of blood in the venous system (so-called backward failure), or both.

The molecular, cellular, and structural changes in the heart that occur as a response to injury, and cause changes in size, shape, and function, are often called left ventricular remodeling. Our discussion focuses on structural changes and considers heart failure to be a progressive disorder, which can culminate in a clinical syndrome characterized by impaired cardiac function and circulatory congestion. Nevertheless, we recognize that the modern treatment of chronic heart failure emphasizes the neurohumoral hypothesis, in which neuroendocrine activation is important in the progression of heart failure. Thus, inhibition of neurohormones may have long-term beneficial effects on morbidity and mortality. \[13\] In the future, patients with CHF may be helped by implanted mechanical cardiac assist devices, an area in which considerable progress has recently been made. \[14\]

**CARDIAC HYPERTROPHY: PATHOPHYSIOLOGY AND PROGRESSION TO FAILURE**

The cardiac myocyte is generally considered a terminally differentiated cell that has lost its ability to divide. Under normal circumstances, functionally useful augmentation of myocyte number (hyperplasia) cannot occur. Increased mechanical load causes an increase in the content of subcellular components and a consequent increase in cell size (hypertrophy). Increased mechanical work owing to pressure or volume overload or trophic signals (e.g., hyperthyroidism through stimulation of beta-adrenergic receptors) increases the rate of protein synthesis, the amount of protein in each cell, the number of sarcomeres and mitochondria, the dimension and mass of myocytes and, consequently, the size of the heart. Nevertheless, the extent to which adult cardiac myocytes have some capacity to synthesize DNA and whether this leads to some degree of cell division is an area of considerable recent attention and debate. \[15\]

The extent of hypertrophy varies for different underlying causes. Heart weight usually ranges from 350 to 600 gm (up to approximately two times normal) in pulmonary hypertension and ischemic heart disease; from 400 to 800 gm (up to two to three times normal) in systemic hypertension, aortic stenosis, mitral regurgitation, or dilated cardiomyopathy; from 600 to 1000 gm (three or more times normal) in aortic regurgitation or hypertrophic cardiomyopathy. Hearts weighing more than 1000 gm are rare.

The pattern of hypertrophy reflects the nature of the stimulus (Fig. 12-3). Pressure-overloaded ventricles (e.g., in hypertension or aortic stenosis) develop pressure-overload (also called concentric) hypertrophy of the left ventricle, with an increased wall thickness. In the left ventricle the augmented muscle may reduce the cavity diameter. In pressure overload, the predominant deposition of sarcomeres is parallel to the long axes of cells; cross-sectional area of myocytes is expanded (but cell length is not). In contrast, volume overload stimulates deposition of new sarcomeres and cell length (as well as width) is increased. Thus, volume-overload hypertrophy is characterized by dilation with increased ventricular diameter. In volume overload, muscle mass and wall thickness are increased approximately in proportion to chamber diameter. However, owing to dilation, wall thickness of a heart in which both hypertrophy and dilation have occurred is
Cardiac hypertrophy is also accompanied by numerous transcriptional and morphologic changes. With prolonged hemodynamic overload, gene expression is altered, leading to re-expression of a pattern of protein synthesis analogous to that seen in fetal cardiac development; other changes are analogous to events that occur during mitosis of normally proliferating cells (Chapter 1). Early mediators of hypertrophy include the immediate-early genes (e.g., c-fos, c-myc, c-jun and EGR1). Selective up-regulation or re-expression of embryonic/fetal forms of contractile and other proteins also occurs, including β-myosin heavy chain, ANP, and collagen (see Chapter 1). The increased myocyte size that occurs in cardiac hypertrophy is usually accompanied by decreased capillary density, increased intercapillary distance, and deposition of fibrous tissue. Nevertheless, the enlarged muscle mass has increased metabolic requirements and increased wall tension, both major determinants of the oxygen consumption of the heart. The other major factors in oxygen consumption are heart rate and contractility (inotropic state, or force of contraction), both of which are often increased in hypertrophic states.

Figure 12-3  Left ventricular hypertrophy. A, Pressure hypertrophy due to left ventricular outflow obstruction. The left ventricle is on the lower right in this apical four-chamber view of the heart. B, Altered cardiac configuration in left ventricular hypertrophy without and with dilation, viewed in transverse heart sections. Compared with a normal heart (center), the pressure-hypertrophied hearts (left and in A) have increased mass and a thick left ventricular wall, but the hypertrophied and dilated heart (right) has increased mass but a normal wall thickness. (Reproduced by permission from Edwards WD: Cardiac anatomy and examination of cardiac specimens. In Emmanouilides GC, Riemenschneider TA, Allen HD, Gutgesell HP (eds): Moss and Adams Heart Disease in Infants, Children, and Adolescents: Including the Fetus and Young Adults, 5th ed. Philadelphia, Williams and Wilkins, 1995, p. 86.)
Thus, the geometry, structure, and composition (cells and extracellular matrix) of the hypertrophied heart are not normal. Cardiac hypertrophy constitutes a tenuous balance between adaptive characteristics (including new sarcomeres) and potentially deleterious structural and biochemical/molecular alterations (including decreased capillary-to-myocyte ratio, increased fibrous tissue, and synthesis of abnormal proteins). Thus, sustained cardiac hypertrophy often evolves to cardiac failure. Ultimately, the primary cardiac disease and the superimposed compensatory burdens further encroach on the myocardial reserve. Then begins the downward slide of stroke volume and cardiac output that often ends in death. The proposed sequence of initially beneficial and later harmful events in the response to increased cardiac work is summarized in Figure 12-4.

Figure 12-4  Schematic representation of the sequence of events in cardiac hypertrophy and its progression to heart failure, emphasizing cellular and extracellular changes.
The structural, biochemical, and molecular basis for myocardial contractile failure is obscure in many cases. Nevertheless, in some instances (e.g., myocardial infarction), there is obvious death of myocytes and loss of vital elements of the "pump"; consequently, noninfarcted regions of cardiac muscle are overworked. In contrast, in valvular heart disease, increased pressure or volume work affects the myocardium globally. The molecular and cellular changes in hypertrophied hearts that initially mediate enhanced function may contribute to the development of heart failure. Proteins related to contractile elements, excitation-contraction coupling, and energy utilization may be significantly altered through production of different isoforms that either may be less functional than normal or may be reduced or increased in amount. Alterations of intracellular handling of calcium ions may also contribute to impaired contraction and relaxation. Loss of myocytes due to apoptosis may contribute to progressive myocardial dysfunction in cardiac disease with hypertrophy.

Increased heart mass predicts excess cardiac mortality and morbidity. Indeed, besides predisposing to CHF, left ventricular hypertrophy is an independent risk factor for sudden death. Interestingly, and in contrast to the pathologic hypertrophy just discussed, hypertrophy that is induced by regular strenuous exercise (physiologic hypertrophy) seems to be an extension of normal growth and has minimal or no deleterious effect. A suitable explanation for this discrepancy is yet lacking.

The degree of structural abnormality of the heart in CHF does not always reflect the level of dysfunction and, indeed, it may be impossible from morphologic examination of the heart to distinguish a damaged but compensated heart from one that has decompensated. At autopsy, the heart of patients having CHF is generally characterized by increased weight, chamber dilation, thin walls, and microscopic changes of hypertrophy, but the extent of these changes varies from one patient to the next. Moreover, many of the significant adaptations and morphologic changes noted in CHF are distant from the heart and are produced by the hypoxic and congestive effects of the failing circulation on other organs and tissues. Thus CHF represents a clinical syndrome characterized primarily by findings outside the cardiovascular system—in both "forward" (e.g., poor organ perfusion) and "backward" (dyspnea and peripheral edema) directions.

To some extent, the right and left sides of the heart act as two distinct anatomic and functional units. Thus left-sided and right-sided failure can occur independently. Nevertheless, because the cardiovascular system is a closed circuit, failure of one side (particularly the left side) often produces excessive strain on the other, terminating in global heart failure. Despite this interdependency, the clearest understanding of the pathologic physiology and anatomy of heart failure is derived from a consideration of each side separately.

### LEFT-SIDED HEART FAILURE

As discussed, left-sided heart failure is most often caused by (1) ischemic heart disease, (2) hypertension, (3) aortic and mitral valvular diseases, and (4) nonischemic myocardial diseases. The morphologic and clinical effects of left-sided CHF primarily result from progressive damming of
blood within the pulmonary circulation and the consequences of diminished peripheral blood pressure and flow.

**Morphology.**

The findings in the heart vary depending on the cause of the disease process; abnormalities such as myocardial infarction or a valvular deformity may be present. Except with obstruction at the mitral valve or other processes that restrict the size of the left ventricle, this chamber is usually hypertrophied and often dilated, sometimes quite massively. There are usually nonspecific changes of hypertrophy and fibrosis in the myocardium. Secondary enlargement of the left atrium with resultant atrial fibrillation (i.e., uncoordinated, chaotic contraction of the atrium) may either compromise stroke volume or cause blood stasis and possible thrombus formation (particularly in the atrial appendage). A fibrillating left atrium carries a substantially increased risk of embolic stroke. The extracardiac effects of left-sided heart failure are manifested most prominently in the lungs, although the kidneys and brain may also be affected.

**Lungs.**

Pressure in the pulmonary veins mounts and is ultimately transmitted retrograde to the capillaries and arteries. The result is pulmonary congestion and edema, with heavy, wet lungs as described in detail in Chapter 4 and Chapter 15. It is sufficient to note here that the pulmonary changes include, in sequence, (1) a perivascular and interstitial transudate, particularly in the interlobular septa, responsible for Kerley's B lines on x-ray; (2) progressive edematous widening of alveolar septa; and (3) accumulation of edema fluid in the alveolar spaces. Moreover, iron-containing proteins in edema fluid and hemoglobin from erythrocytes, which leak from congested capillaries, are phagocytosed by macrophages and converted to hemosiderin. Hemosiderin-containing macrophages in the alveoli (called siderophages, or heart failure cells) denote previous episodes of pulmonary edema.

These anatomic changes are associated with striking clinical manifestations. **Dyspnea** (breathlessness), usually the earliest and the cardinal complaint of patients in left-sided heart failure, is an exaggeration of the normal breathlessness that follows exertion. With further impairment, there is **orthopnea**, which is dyspnea on lying down that is relieved by sitting or standing. Thus the orthopneic patient must sleep while sitting upright. **Paroxysmal nocturnal dyspnea** is an extension of orthopnea that consists of attacks of extreme dyspnea bordering on suffocation, usually occurring at night. Cough is a common accompaniment of left-sided failure.

**Kidneys.**

Decreased cardiac output causes a reduction in renal perfusion, which activates the renin-angiotensin-andosterone system, inducing retention of salt and water with consequent expansion of the interstitial fluid and blood volumes. This compensatory reaction can contribute to the pulmonary edema in left-sided heart failure and is counteracted by the release of ANP through atrial dilation, which acts to decrease excessive blood volume. If the perfusion deficit of the kidney becomes sufficiently severe, impaired excretion of nitrogenous products may cause azotemia, in this instance **prerenal azotemia** (Chapter 20).
Brain.

In far-advanced CHF, cerebral hypoxia may give rise to hypoxic encephalopathy (see Chapter 28), with irritability, loss of attention span, and restlessness, which may even progress to stupor and coma.

RIGHT-SIDED HEART FAILURE

Isolated right-sided heart failure occurs in only a few diseases. Usually it is a secondary consequence of left-sided heart failure because any increase in pressure in the pulmonary circulation incidental to left-sided heart failure inevitably produces an increased burden on the right side of the heart. The causes of right-sided heart failure must then include all those that induce left-sided heart failure.

Pure right-sided heart failure most often occurs with chronic severe pulmonary hypertension and thus is called cor pulmonale. In this condition, the right ventricle is burdened by a pressure workload due to increased resistance within the pulmonary circulation. Hypertrophy and dilation are generally confined to the right ventricle and atrium, although bulging of the ventricular septum to the left can cause dysfunction of the left ventricle.

The major morphologic and clinical effects of pure right-sided heart failure differ from those of left-sided heart failure in that pulmonary congestion is minimal, whereas engorgement of the systemic and portal venous systems may be pronounced.

Morphology.

Liver and Portal System.

The liver is usually increased in size and weight (congestive hepatomegaly), and a cut section displays prominent passive congestion (see Chapter 18). Congested red centers of the liver lobules are surrounded by paler, sometimes fatty, peripheral regions. In some instances, especially when left-sided heart failure is also present, the severe central hypoxia produces centrilobular necrosis along with the sinusoidal congestion. With long-standing severe right-sided heart failure, the central areas can become fibrotic, creating so-called cardiac sclerosis or cardiac cirrhosis (Chapter 18).

Right-sided heart failure also leads to elevated pressure in the portal vein and its tributaries. Congestion produces a tense, enlarged spleen (congestive splenomegaly). Microscopically there may be marked sinusoidal dilation. With long-standing congestion, the enlarged spleen may achieve a weight of 300 to 500 gm (normal, approximately 150 gm). Chronic edema of the bowel wall can also occur and in some patients may interfere with absorption of nutrients. In addition, accumulations of transudate in the peritoneal cavity may give rise to ascites.

Kidneys.

Congestion of the kidneys is more marked with right-sided heart failure than with left-sided heart failure, leading to greater fluid retention, peripheral edema, and more pronounced azotemia.
Brain.

Symptoms essentially identical to those described in left-sided heart failure may occur, representing venous congestion and hypoxia of the central nervous system.

Pleural and Pericardial Spaces.

Accumulation of fluid in the pleural space (particularly right) and pericardial space (effusions) may appear. Thus, while pulmonary edema indicates left-sided heart failure, pleural effusions accompany right-sided heart failure. Pleural effusions can range from 100 ml to well over 1 liter and can cause partial atelectasis of the corresponding lung.

Subcutaneous Tissues.

Peripheral edema of dependent portions of the body, especially ankle (pedal) and pretibial edema, is a hallmark of right-sided heart failure. In chronically bedridden patients, the edema may be primarily presacral. Generalized massive edema is called anasarca.

The symptoms of pure left-sided heart failure are largely due to pulmonary congestion and edema. In contrast, in right-sided heart failure, respiratory symptoms may be absent or quite insignificant, and there is a systemic (and portal) venous congestive syndrome, with hepatic and splenic enlargement, peripheral edema, pleural effusion, and ascites. In many cases of chronic cardiac decompensation, however, the patient presents with the picture of biventricular CHF, encompassing the clinical syndromes of both right-sided and left-sided heart failure.