Heart Failure

David Miranda
Gregory D. Lewis
Michael A. Fifer

9

Chapter Outline

The heart normally accepts blood at low filling pressures during diastole and then propels it forward at higher pressures in systole. Heart failure is present when the heart is unable to pump blood forward at a sufficient rate to meet the metabolic demands of the body or is able to do so only if cardiac filling pressures are abnormally high. Although conditions outside the heart may cause this definition to be met through inadequate tissue perfusion (e.g., severe hemorrhage) or increased metabolic demands (e.g., hyperthyroidism), in this chapter, only cardiac causes of heart failure are considered.

Heart failure results in a clinical syndrome of fatigue, shortness of breath, and often volume overload. It may be the final and most severe manifestation of nearly every form of cardiac disease, including coronary atherosclerosis, myocardial infarction, valvular diseases, hypertension, congenital heart disease, and the cardiomyopathies. More than 550,000 new cases are diagnosed each year in the United States, where the current prevalence is approximately 5.8 million. The number of patients with heart failure is increasing, not only because the population is aging but also because of interventions that prolong survival after damaging cardiac insults such as myocardial infarction. As a result, heart failure now accounts for more than 12 million medical office visits annually and is the most common diagnosis of hospitalized patients aged 65 years and older.

Heart failure most commonly results from conditions of impaired left ventricular function. Thus, this chapter begins by reviewing the physiology of normal myocardial contraction and relaxation.

PHYSIOLOGY

Experimental studies of isolated cardiac muscle segments have revealed several important principles that can be applied to the intact heart. As a muscle segment is stretched apart, the relation between its length and the tension it passively develops is curvilinear, reflecting its intrinsic elastic properties (Fig. 9-1A, lower curve). If the muscle is first passively stretched and then stimulated to contract while its ends are held at fixed

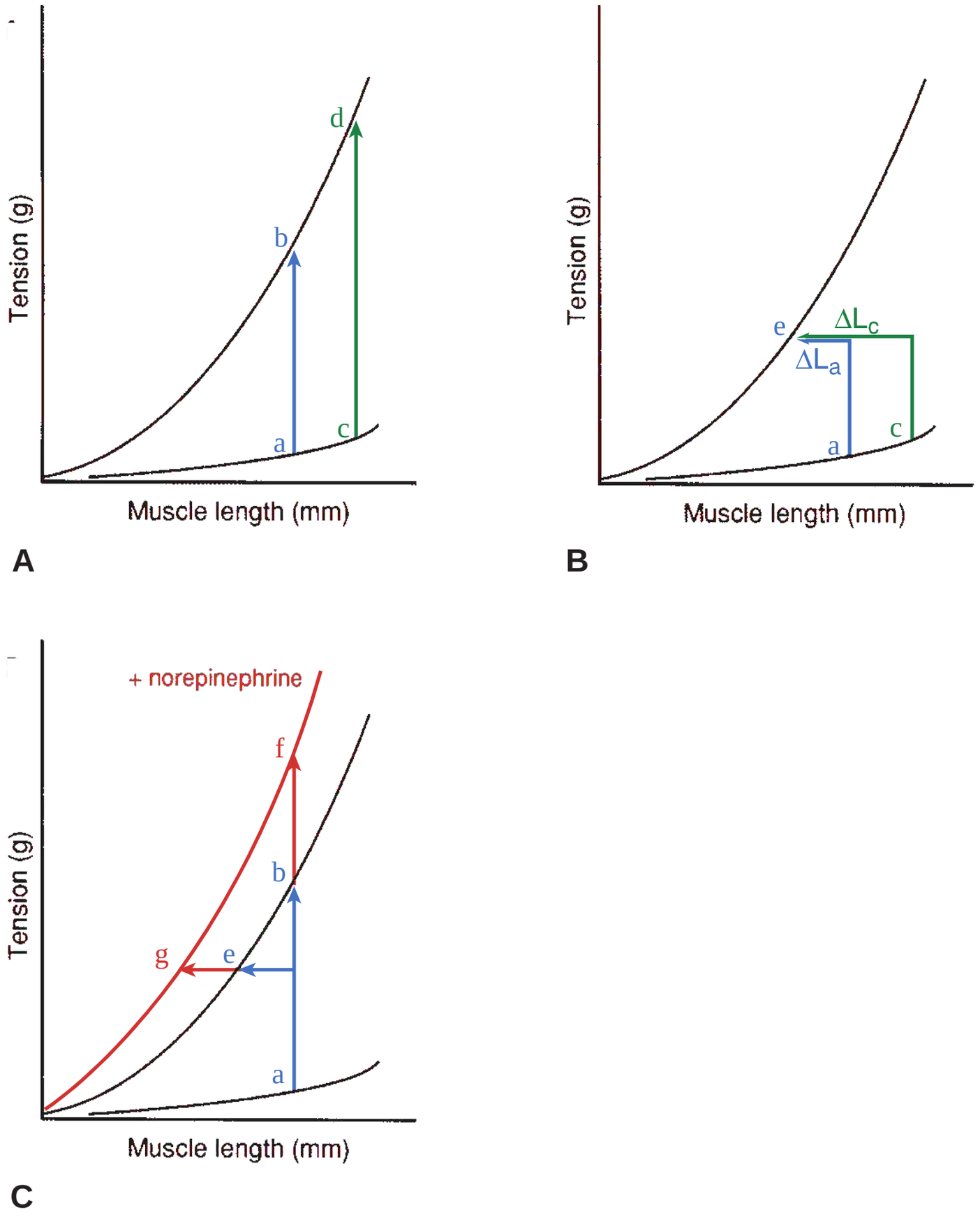

FIGURE 9-1. Physiology of normal cardiac muscle segments. A. Passive (lower curve) and total (upper curve) length–tension relations for isolated cat papillary muscle. Lines ab and cd represent the force developed during isometric contractions. Initial passive muscle length c is longer (i.e., has been stretched more) than length a and therefore has a greater passive tension. When the muscle segments are stimulated to contract, the muscle with the longer initial length generates greater total tension (point d vs. point b). **B.** If the muscle fiber preparation is allowed to shorten against a fixed load, the length at the end of the contraction is dependent on the load but not the initial fiber length; stimulation at point a or c results in the same final fiber length (e). Thus, the muscle that starts at length c shortens a greater distance (ΔL_c) than the muscle at length a (ΔL_a). **C.** The uppermost curve is the length–tension relation in the presence of the positive inotropic agent norepinephrine. For any given initial length, an isometric contraction in the presence of norepinephrine generates greater force (point f) than one in the absence of norepinephrine (point b). When contracting against a fixed load, the presence of norepinephrine causes greater muscle fiber shortening and a smaller final muscle length (point g) compared with contraction in the absence of the inotropic agent (point e). (Adapted from Downing SE, Sonnenblick EH. Cardiac muscle mechanics and ventricular performance: force and time parameters. Am J Physiol. 1964;207:705–715.)

positions (termed an isometric contraction), the total tension (the sum of active plus passive tension) generated by the fibers is proportional to the length of the muscle at the time of stimulation (see Fig. 9-1A, upper curve). That is, stretching the muscle before stimulation optimizes the overlap and interaction of myosin and actin filaments, increasing the number of cross bridges and the force of contraction. Stretching cardiac muscle fibers also increases the sensitivity of the myofilaments to calcium, which further augments force development.

This relationship between the initial fiber length and force development is of great importance in the intact heart: within a physiologic range, the larger the ventricular volume during diastole, the more the fibers are stretched before stimulation and the greater the force of the next contraction. This is the basis of the **Frank–Starling relationship**, the observation that ventricular output increases in relation to the **preload** (the stretch on the myocardial fibers before contraction).

A second observation from isolated muscle experiments arises when the fibers are not tethered at a fixed length but are allowed to shorten during stimulation against a fixed load (termed the **afterload**). In this situation (termed an isotonic contraction), the final length of the muscle at the end of contraction is determined by the magnitude of the load but is independent of the length of the muscle before stimulation (see Fig. 9-1B). That is, (1) the tension generated by the fiber is equal to the fixed load; (2) the greater the load opposing contraction, the less the muscle fiber can shorten; (3) if the fiber is stretched to a longer length before stimulation but the afterload is kept constant, the muscle will shorten a greater distance to attain the same final length at the end of contraction; and (4) the maximum tension that can be produced during isotonic contraction (i.e., using a load sufficiently great such that the muscle is just unable to shorten) is the same as the force produced by an isometric contraction at that initial fiber length.

This concept of afterload is also relevant to the intact heart: the pressure generated by the ventricle and the size of the chamber at the end of each contraction depend on the load against which the ventricle contracts but are independent of the stretch on the myocardial fibers before contraction.

A third key experimental observation relates to myocardial **contractility**, which accounts for changes in the force of contraction independent of the initial fiber length and afterload. Contractility reflects chemical and hormonal influences on cardiac contraction, such as exposure to catecholamines. When contractility is enhanced pharmacologically (e.g., by a norepinephrine infusion), the relation between initial fiber length and force developed during contraction is shifted upward (see Fig. 9-1C) such that a greater total tension develops with isometric contraction at any given preload. Similarly, when contractility is augmented and the cardiac muscle is allowed to shorten against a fixed afterload, the fiber contracts to a greater extent and achieves a shorter final fiber length compared with the baseline state. At the molecular level, enhanced contractility is likely related to an increased cycling rate of actin–myosin cross-bridge formation.

Determinants of Contractile Function in the Intact Heart

In a healthy person, cardiac output is matched to the body's total metabolic need. Cardiac output (CO) is equal to the product of stroke volume (SV, the volume of blood ejected with each contraction) and the heart rate (HR):

$$CO = SV \times HR$$

The three major determinants of stroke volume are preload, afterload, and myocardial contractility, as shown in Figure 9-2.

Preload

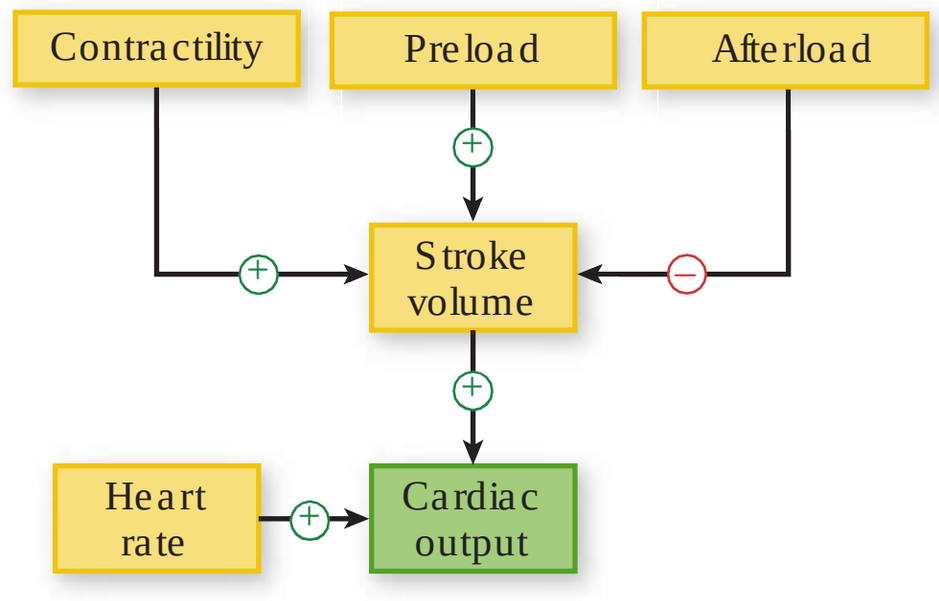

FIGURE 9-2. Key mediators of cardiac output. Determinants of the stroke volume include contractility, preload, and afterload. Cardiac output = heart rate × stroke volume.

The concept of preload (Table 9-1) in the intact heart was described by physiologists Frank and Starling a century ago. In experimental preparations, they showed that within physiologic limits, the more a normal ventricle is distended (i.e., filled with blood) during diastole, the greater the volume that is ejected during the next systolic contraction. This relationship is illustrated graphically by the Frank–Starling curve, also known as the ventricular function curve (Fig. 9-3). The graph relates a measurement of cardiac performance (such as cardiac output or stroke volume) on the vertical axis as a function of preload on the horizontal axis. As described earlier, the preload can be thought of as the amount of myocardial stretch at the end of diastole, just before contraction. Measurements that correlate with myocardial stretch, and that are often used to indicate the preload on the horizontal axis, are the ventricular end-diastolic volume (EDV) or end-diastolic pressure (EDP). Conditions that decrease intravascular volume, and thereby reduce ventricular preload (e.g., dehydration or severe hemorrhage), result in a smaller EDV and hence a reduced stroke volume during contraction. Conversely, an increased volume within the left ventricle during diastole (e.g., a large intravenous fluid infusion) results in a greater-than-normal stroke volume.

TABLE 9-1 Terms Related to Cardiac Performance

Term	Definition
Preload	The ventricular wall tension at the end of diastole. In clinical terms, it is the stretch on the ventricular fibers just before contraction, often approximated by the end-diastolic volume or end-diastolic pressure.
Afterload	The ventricular wall tension during contraction; the force that must be overcome for the ventricle to eject its contents. Often approximated by the systolic ventricular (or arterial) pressure
Contractility (inotropic state)	Property of heart muscle that accounts for changes in the strength of contraction, independent of the preload and afterload. Reflects chemical or hormonal influences (e.g., catecholamines) on the force of contraction
Stroke volume (SV)	Volume of blood ejected from the ventricle during systole SV = End-diastolic volume – end-systolic volume
Ejection fraction (EF)	The fraction of end-diastolic volume ejected from the ventricle during each systolic contraction (normal range = 55%–75%) EF = Stroke volume ÷ end-diastolic volume
Cardiac output (CO)	Volume of blood ejected from the ventricle per minute CO = SV × Heart rate
Compliance	Intrinsic property of a chamber that describes its pressure–volume relationship during filling. Reflects the ease or difficulty with which the chamber can be filled. Compliance = Δ volume ÷ Δ pressure

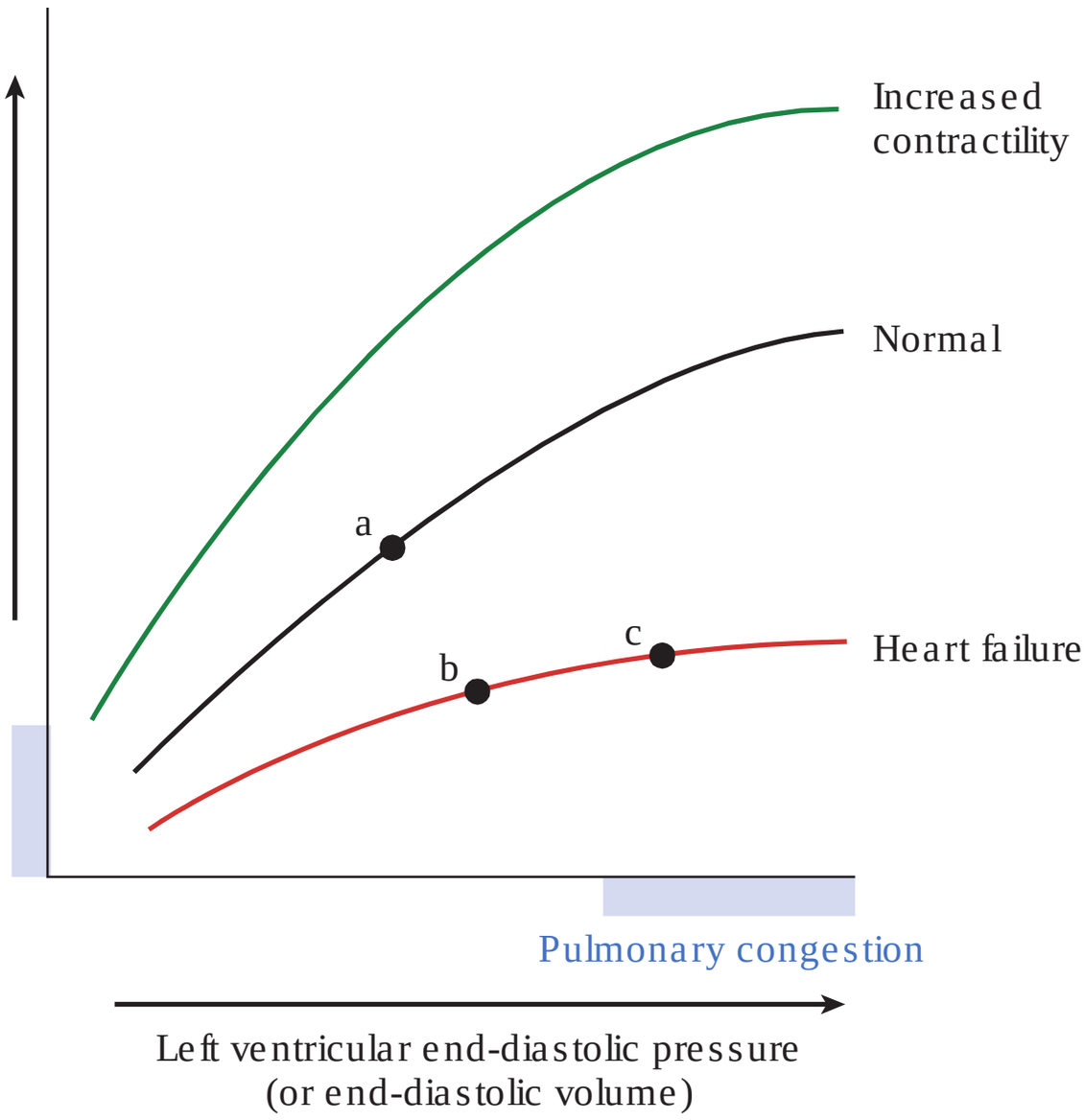

FIGURE 9-3. Left ventricular (LV) performance (Frank–Starling) curves relate preload, measured as LV end-diastolic volume (EDV) or pressure (EDP), to cardiac performance, measured as ventricular stroke volume or cardiac output. On the curve of a normal heart (middle line), cardiac performance continuously increases as a function of preload. States of increased contractility (e.g., norepinephrine infusion) are characterized by an augmented stroke volume at any level of preload (upper line). Conversely, decreased LV contractility (commonly associated with heart failure) is characterized by a curve that is shifted downward (lower line). Point a is an example of a normal person at rest. Point b represents the same person after developing systolic dysfunction and heart failure (e.g., after a large myocardial infarction): stroke volume has fallen, and the decreased LV emptying results in elevation of the EDV. Because point b is on the ascending portion of the curve, the elevated EDV serves a compensatory role because it results in an increase in subsequent stroke volume, albeit much less than if operating on the normal curve. Further augmentation of LV filling (e.g., increased circulating volume) in the heart failure patient is represented by point c, which resides on the relatively flat part of the curve: stroke volume is only slightly augmented, but the significantly increased EDP results in pulmonary congestion.

Afterload

Afterload (see Table 9-1) in the intact heart reflects the resistance that the ventricle must overcome to empty its contents. It is more formally defined as the ventricular wall stress that develops during systolic ejection. Wall stress (σ), like pressure, is expressed as force per unit area and, for the left ventricle, may be estimated from Laplace relationship:

$$s = \frac{P \times r}{2h}$$

where P is ventricular pressure, r is ventricular chamber radius, and h is ventricular wall thickness. Thus, ventricular wall stress rises in response to a higher pressure load (e.g., hypertension) or an increased chamber size (e.g., a dilated left ventricle). Conversely, as would be expected from Laplace relationship, an increase in wall thickness (h) serves a compensatory role in reducing wall stress, because the force is distributed over a greater mass per unit surface area of ventricular muscle.

Contractility (Also Termed "Inotropic State")

In the intact heart, as in the isolated muscle preparation, contractility accounts for changes in myocardial force for a given set of preload and afterload conditions, resulting from chemical

and hormonal influences. By relating a measure of ventricular performance (stroke volume or cardiac output) to preload (left ventricular EDP or EDV), each Frank–Starling curve is a reflection of the heart's current inotropic state (see Fig. 9-3). The effect on stroke volume by an alteration in preload is reflected by a change in position along a particular Frank–Starling curve. Conversely, a change in contractility shifts the entire curve in an upward or downward direction. Thus, when contractility is enhanced pharmacologically (e.g., by an infusion of norepinephrine), the ventricular performance curve is displaced upward such that at any given preload, the stroke volume is increased. Conversely, when a drug that reduces contractility is administered, or the ventricle's contractile function is impaired (as in certain types of heart failure), the curve shifts in a downward direction, leading to reductions in stroke volume and cardiac output at any given preload.

Pressure–Volume Loops

Another useful graphic display to illustrate the determinants of cardiac function is the ventricular pressure–volume loop, which relates changes in ventricular volume to corresponding changes in pressure throughout the cardiac cycle (Fig. 9-4). In the left ventricle, filling of the chamber begins after the mitral valve opens in early diastole (point a). The curve between points a and b represents diastolic filling. As the volume increases during diastole,

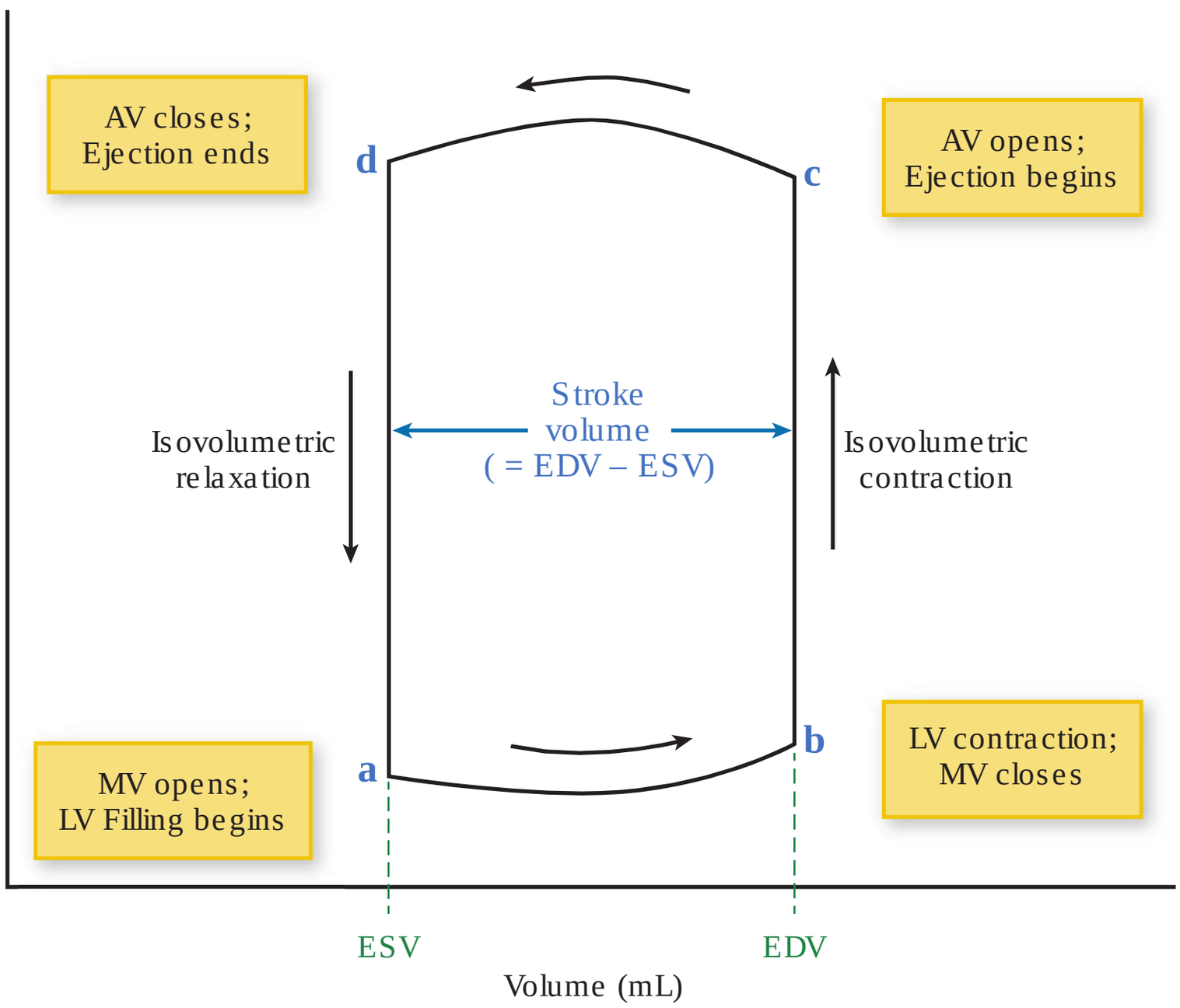

FIGURE 9-4. Example of a normal left ventricular (LV) pressure–volume loop. At point a, the mitral valve (MV) opens and filling of the LV commences. During passive diastolic filling of the LV (line ab), its volume increases with a gradual rise in pressure. When ventricular contraction commences and its pressure exceeds that of the left atrium, the MV closes (point b) and isovolumetric contraction of the LV ensues (the aortic valve is not yet open, and no blood leaves the chamber), as shown by line bc. When LV pressure rises to that in the aorta, the aortic valve (AV) opens (point c) and ejection begins. The volume within the LV declines during ejection (line cd), but LV pressure continues to rise until ventricular relaxation commences, then it begins to lessen. At point d, the LV pressure during relaxation falls below that in the aorta, and the AV closes, leading to isovolumetric relaxation (line da). As LV pressure declines further to below that in the left atrium, the MV reopens (point a). Point b represents the end-diastolic volume (EDV) and pressure, and point d is the end-systolic volume (ESV) and pressure. Stroke volume is calculated as the difference between the EDV and ESV.

it is associated with a small rise in pressure, in accordance with the passive length–tension properties or **compliance** (see Table 9-1) of the myocardium, analogous to the lower curve in Figure 9-1A for an isolated muscle preparation.

Next, the onset of left ventricular systolic contraction causes the ventricular pressure to rise. When the pressure in the left ventricle (LV) exceeds that of the left atrium (point b), the mitral valve is forced to close. As the pressure continues to increase, the ventricular volume does not immediately change, because the aortic valve has not yet opened; therefore, this phase is called **isovolumetric contraction**. When the rise in ventricular pressure reaches the aortic diastolic pressure, the aortic valve is forced to open (point c) and ejection of blood into the aorta commences. During ejection, the volume within the ventricle decreases, but its pressure continues to rise until ventricular relaxation begins. The pressure against which the ventricle ejects (a component of afterload) is represented by the curve cd. Ejection ends during the relaxation phase, when the ventricular pressure falls below that of the aorta and the aortic valve closes (point d).

As the ventricle continues to relax, its pressure declines while its volume remains constant because the mitral valve has not yet opened (this phase is known as **isovolumetric relaxation**). When the ventricular pressure falls below that of the left atrium, the mitral valve opens again (point a) and the cycle repeats.

Note that point b represents the pressure and volume at the end of diastole, whereas point d represents the pressure and volume at the end of systole. The difference between the EDV and end-systolic volume (ESV) represents the quantity of blood ejected during contraction (i.e., the stroke volume).

Changes in any of the determinants of cardiac function are reflected by alterations in the pressure–volume loop. By analyzing the effects of a change in an individual parameter (preload, afterload, or contractility) on the pressure–volume relationship, the resulting modif cations in ventricular pressure and stroke volume can be predicted (Fig. 9-5).

Alterations in Preload

If afterload and contractility are held constant but preload is caused to increase (e.g., by administration of intravenous fluid), left ventricular EDV rises. This increase in preload augments the stroke volume via the Frank–Starling mechanism such that the ESV achieved is the same as it was before increasing the preload (see Fig. 9-5A). This means that the normal left ventricle is able to adjust its stroke volume and effectively empty its contents to match its diastolic f lling volume, as long as contractility and afterload are kept constant.

Although EDV and EDP are often used interchangeably as markers of preload, the relationship between f lling volume and pressure (i.e., ventricular compliance; see Table 9-1) largely governs the extent of ventricular f lling. If ventricular compliance is reduced (e.g., in severe LV hypertrophy), the slope of the diastolic f lling curve (segment ab in Fig. 9-4) becomes steeper. A “stiff” or poorly compliant ventricle reduces the ability of the chamber to f ll during diastole, resulting in a lower-than-normal ventricular EDV. In this circumstance, the stroke volume will be reduced while the ESV remains unchanged.

Alterations in Afterload

If preload and contractility are held constant and afterload is augmented (e.g., in high-impedance states such as hypertension or aortic stenosis), the pressure generated by the left ventricle during ejection increases. In this situation, more ventricular work is expended in overcoming the resistance to ejection and therefore less f ber shortening takes place. As shown in Figure 9-5B, an increase in afterload results in a higher ventricular systolic pressure and a greater-than-normal LV ESV. Thus, in the setting of increased afterload, the ventricular stroke volume (EDV-ESV) is reduced.

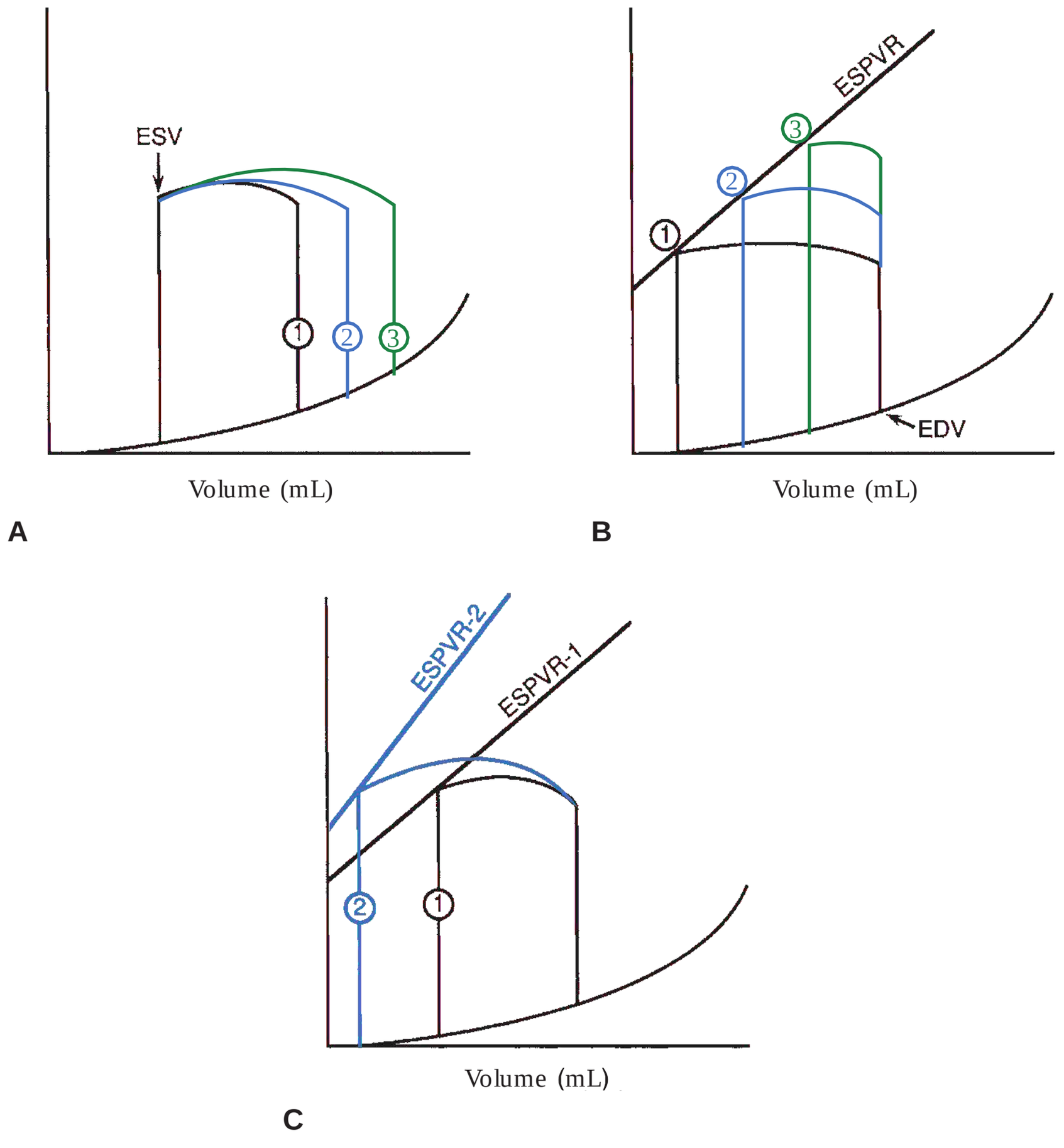

FIGURE 9-5. The effect of varying preload, afterload, and contractility on the pressure–volume loop. **A.** When arterial pressure (afterload) and contractility are held constant, sequential increases (lines 1, 2, and 3) in preload (measured in this case as end-diastolic volume [EDV]) are associated with loops that have progressively higher stroke volumes but a constant end-systolic volume (ESV). **B.** When the preload (EDV) and contractility are held constant, sequential increases (points 1, 2, and 3) in arterial pressure (afterload) are associated with loops that have progressively lower stroke volumes and higher end-systolic volumes. There is a nearly linear relationship between the afterload and ESV, termed the end-systolic pressure–volume relation (ESPVR). **C.** A positive inotropic intervention shifts the end-systolic pressure–volume relation upward and leftward from ESPVR-1 to ESPVR-2, resulting in loop 2, which has a larger stroke volume and a smaller end-systolic volume than the original loop 1.

The dependence of the ESV on afterload is approximately linear: the greater the afterload, the higher the ESV. This relationship is depicted in Figure 9-5 as the **end-systolic pressure–volume relation (ESPVR)** and is analogous to the total tension curve in the isolated muscle experiments described earlier.

Alterations in Contractility

The slope of the ESPVR line on the pressure–volume loop graph is a function of cardiac contractility. In conditions of increased contractility, the ESPVR slope becomes steeper; that is, it shifts upward and toward the left. Hence, at any given preload or afterload, the ventricle empties more completely (the stroke volume increases) and results in a smaller-than-normal ESV (see Fig. 9-5C). Conversely, in situations of reduced contractility, the ESPVR line shifts

downward, consistent with a decline in stroke volume and a higher ESV. Thus, the ESV is dependent on the afterload against which the ventricle contracts and the inotropic state, but is independent of the EDV prior to contraction.

The important physiologic concepts in this section are summarized here:

1. Ventricular stroke volume is a function of preload, afterload, and contractility. SV rises when there is an increase in preload, a decrease in afterload, or augmented contractility.
2. Ventricular EDV (or EDP) is used as a representation of preload. The EDV is influenced by the chamber's compliance.
3. Ventricular ESV depends on the afterload and contractility but not on the preload.

PATHOPHYSIOLOGY

Chronic heart failure may result from a wide variety of cardiovascular insults. The etiologies can be grouped into those that (1) impair ventricular contractility, (2) increase afterload, or (3) impair ventricular relaxation and f lling (Fig. 9-6). Heart failure that results from an abnormality of ventricular emptying (due to impaired contractility or greatly excessive afterload) is termed systolic dysfunction, whereas heart failure caused by abnormalities of diastolic relaxation or ventricular f lling is termed diastolic dysfunction. However, there is much overlap, and many patients demonstrate both systolic and diastolic abnormalities. As a result, it is common to categorize heart failure patients into two general categories

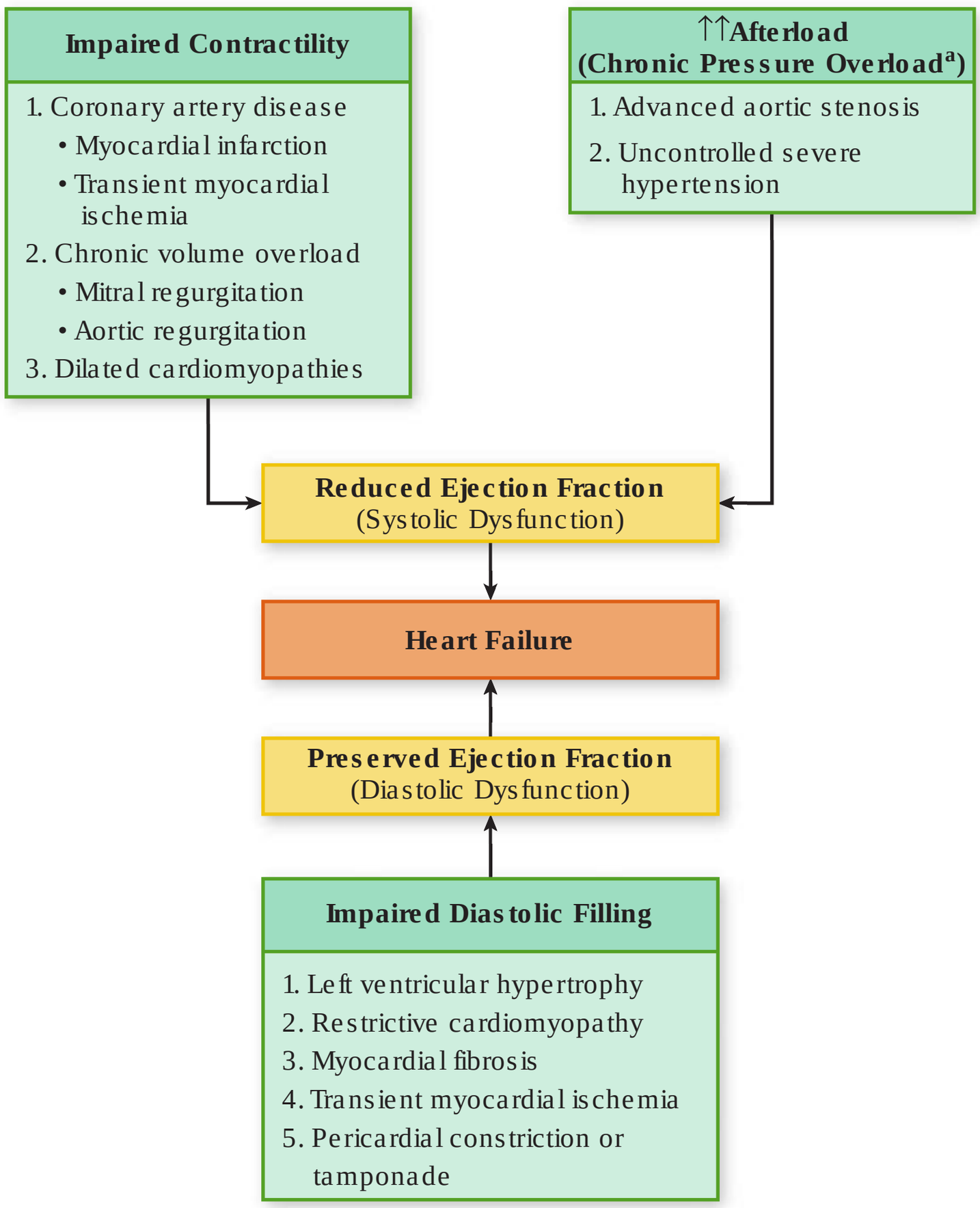

FIGURE 9-6. Conditions that cause left-sided heart failure through impairment of ventricular systolic or diastolic function.
[a]Note that in chronic stable stages, the conditions in this box (aortic stenosis, hypertension) may instead result in heart failure with preserved EF, due to compensatory ventricular hypertrophy and increased diastolic stiffness (diastolic dysfunction).

based on the left ventricular ejection fraction (EF), a measure of cardiac performance (see Table 9-1): (1) **heart failure with reduced EF** (i.e., primarily systolic dysfunction) and (2) **heart failure with preserved EF** (i.e., primarily diastolic dysfunction). In the United States, approximately one half of patients with heart failure fall into each of these categories.

Heart Failure with Reduced EF

In states of systolic dysfunction, the affected ventricle has a diminished capacity to eject blood because of impaired myocardial contractility or pressure overload (i.e., excessive afterload). Loss of contractility may result from destruction of myocytes, abnormal myocyte function, or fibrosis. Pressure overload impairs ventricular ejection by significantly increasing resistance to flow.

Figure 9-7A depicts the effects of systolic dysfunction due to impaired contractility on the pressure–volume loop. The ESPVR is shifted downward such that systolic emptying ceases at a higher-than-normal ESV. As a result, the stroke volume falls. When normal pulmonary venous return is added to the increased ESV that has remained in the ventricle because of incomplete emptying, the diastolic chamber volume increases, resulting in a higher-than-normal EDV and pressure. While that increase in preload induces a compensatory rise in stroke volume (via the Frank–Starling mechanism), impaired contractility and the reduced EF cause the ESV to remain elevated.

During diastole, the persistently elevated LV pressure is transmitted to the left atrium (through the open mitral valve) and to the pulmonary veins and capillaries. An elevated pulmonary capillary hydrostatic pressure, when sufficiently high (usually greater than 20 mm Hg), results in the transudation of fluid into the pulmonary interstitium and symptoms of pulmonary congestion.

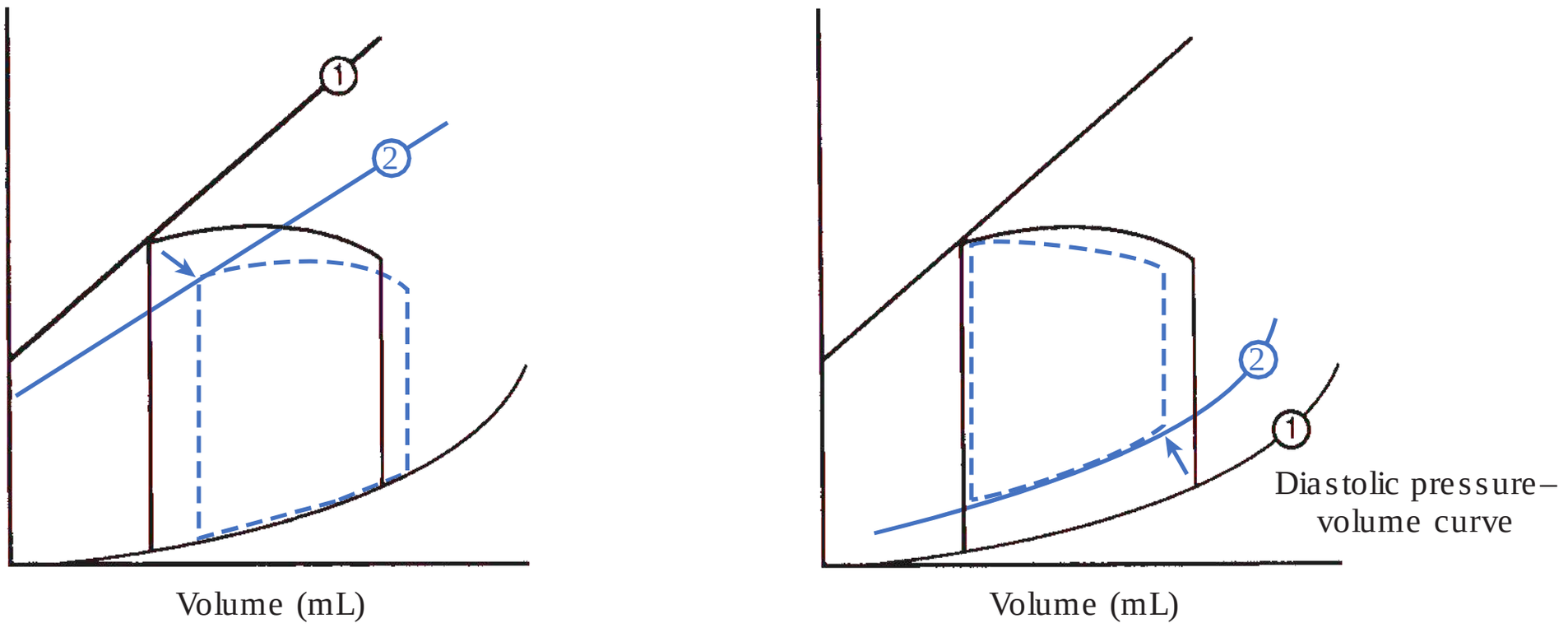

FIGURE 9-7. The pressure–volume loop in systolic and diastolic dysfunction. A. The normal pressure–volume loop (solid line) is compared with one demonstrating systolic dysfunction (dashed blue line). In systolic dysfunction caused by decreased cardiac contractility, the end-systolic pressure–volume relation is shifted downward and rightward (from line 1 to line 2). As a result, the end-systolic volume (ESV) is increased (arrow). As normal venous return is added to that greater-than-normal ESV, there is an obligatory increase in the end-diastolic volume (EDV) and pressure (preload), which serves a compensatory function by partially elevating stroke volume toward normal via the Frank–Starling mechanism. **B.** The pressure–volume loop of diastolic dysfunction resulting from increased stiffness of the ventricle (dashed blue line). The passive diastolic pressure–volume curve is shifted upward (from line 1 to line 2) such that at any diastolic volume, the ventricular pressure is higher than normal. The result is a decreased EDV (arrow) because of reduced filling of the stiffened ventricle at a higher-than-normal end-diastolic pressure.

Heart Failure with Preserved EF

Patients who exhibit heart failure with preserved EF frequently demonstrate abnormalities of ventricular diastolic function: impaired early diastolic relaxation (an active, energy-dependent process), increased stiffness of the ventricular wall (a passive property), or both. Acute myocardial ischemia is an example of a condition that transiently inhibits energy delivery and diastolic relaxation. Conversely, left ventricular hypertrophy, fibrosis, or restrictive cardiomyopathy (see Chapter 10) causes the LV walls to become chronically stiffened. Certain pericardial diseases (cardiac tamponade and pericardial constriction, as described in Chapter 14) present an external force that limits ventricular filling and represent potentially reversible forms of diastolic dysfunction. The effect of impaired diastolic function is reflected in the pressure–volume loop (see Fig. 9-7B): in diastole, filling of the ventricle occurs at higher-than-normal pressures because the lower part of the loop is shifted upward as a result of reduced chamber compliance. Patients with diastolic dysfunction often manifest signs of vascular congestion because the elevated diastolic pressure is transmitted retrograde to the pulmonary and systemic veins.

Right-Sided Heart Failure

Whereas the physiologic principles described above may be applied to both right-sided and left-sided heart failure, there are distinct differences in function between the two ventricles. Compared with the left ventricle, the right ventricle (RV) is a thin-walled, highly compliant chamber that accepts its blood volume at low pressures and ejects against a low pulmonary vascular resistance. As a result of its high compliance, the RV has little difficulty accepting a wide range of filling volumes without marked changes in its filling pressure. Conversely, the RV is quite susceptible to failure in situations that present a sudden increase in afterload, such as acute pulmonary embolism.

The most common cause of right-sided heart failure is actually the presence of left-sided heart failure (Table 9-2). In this situation, excessive afterload confronts the RV because of the elevated pulmonary vascular pressures that result from LV dysfunction. Isolated right heart failure is less common and usually reflects increased RV afterload owing to diseases of the lung parenchyma or pulmonary vasculature. Right-sided heart disease that results from a primary pulmonary process is known as cor pulmonale, which may lead to symptoms of right heart failure.

When the RV fails, the elevated diastolic pressure is transmitted retrograde to the right atrium with subsequent congestion of the systemic veins, accompanied by signs of right-sided heart failure as described below. Indirectly, isolated right heart failure may also influence left heart function: the decreased right ventricular output reduces blood return to the LV (i.e., diminished preload), causing left ventricular stroke volume to decline.

TABLE 9-2 Examples of Conditions That Cause Right-Sided Heart Failure

Cardiac causes
Left-sided heart failure
Pulmonic valve stenosis
Right ventricular infarction
Pulmonary parenchymal diseases
Chronic obstructive pulmonary disease
Interstitial lung disease (e.g., sarcoidosis)
Chronic lung infection or bronchiectasis
Pulmonary vascular diseases
Pulmonary embolism
Pulmonary arteriolar hypertension

COMPENSATORY MECHANISMS

Several natural compensatory mechanisms are called into action in patients with heart failure that buffer the fall in cardiac output and help preserve suff cient blood pressure (BP) to perfuse vital organs. These compensations include (1) the Frank–Starling mechanism, (2) neurohormonal alterations, and (3) the development of ventricular hypertrophy and remodeling (Fig. 9-8).

Frank–Starling Mechanism

As shown in Figure 9-3, heart failure caused by impaired left ventricular contractile function causes a downward shift of the ventricular performance curve. Consequently, at a given preload, stroke volume is decreased compared with normal. The reduced stroke volume results in incomplete chamber emptying, so that the volume of blood that accumulates in the ventricle during diastole is higher than normal (see Fig. 9-3, point b). This increased stretch on the myof bers, acting via the Frank–Starling mechanism, induces a greater stroke volume on subsequent contraction, which helps to empty the enlarged left ventricle and preserve forward cardiac output (see Fig. 9-8).

This benef cial compensatory mechanism has its limits, however. In the case of severe heart failure with marked depression of contractility, the curve may be nearly flat at higher diastolic volumes, reducing the augmentation of cardiac output achieved by the increased chamber f lling. Concurrently in such a circumstance, marked elevation of the EDV and pressure (which is transmitted retrograde to the left atrium, pulmonary veins, and capillaries) may result in pulmonary congestion and edema (see Fig. 9-3, point c).

Neurohormonal Alterations

Several important neurohormonal compensatory mechanisms are activated in heart failure in response to the decreased cardiac output (Fig. 9-9). Three of the most important involve (1) the adrenergic nervous system, (2) the renin–angiotensin–aldosterone system, and (3) increased production of antidiuretic hormone (ADH). In part, these mechanisms serve to increase systemic vascular resistance, which helps to maintain arterial perfusion to vital

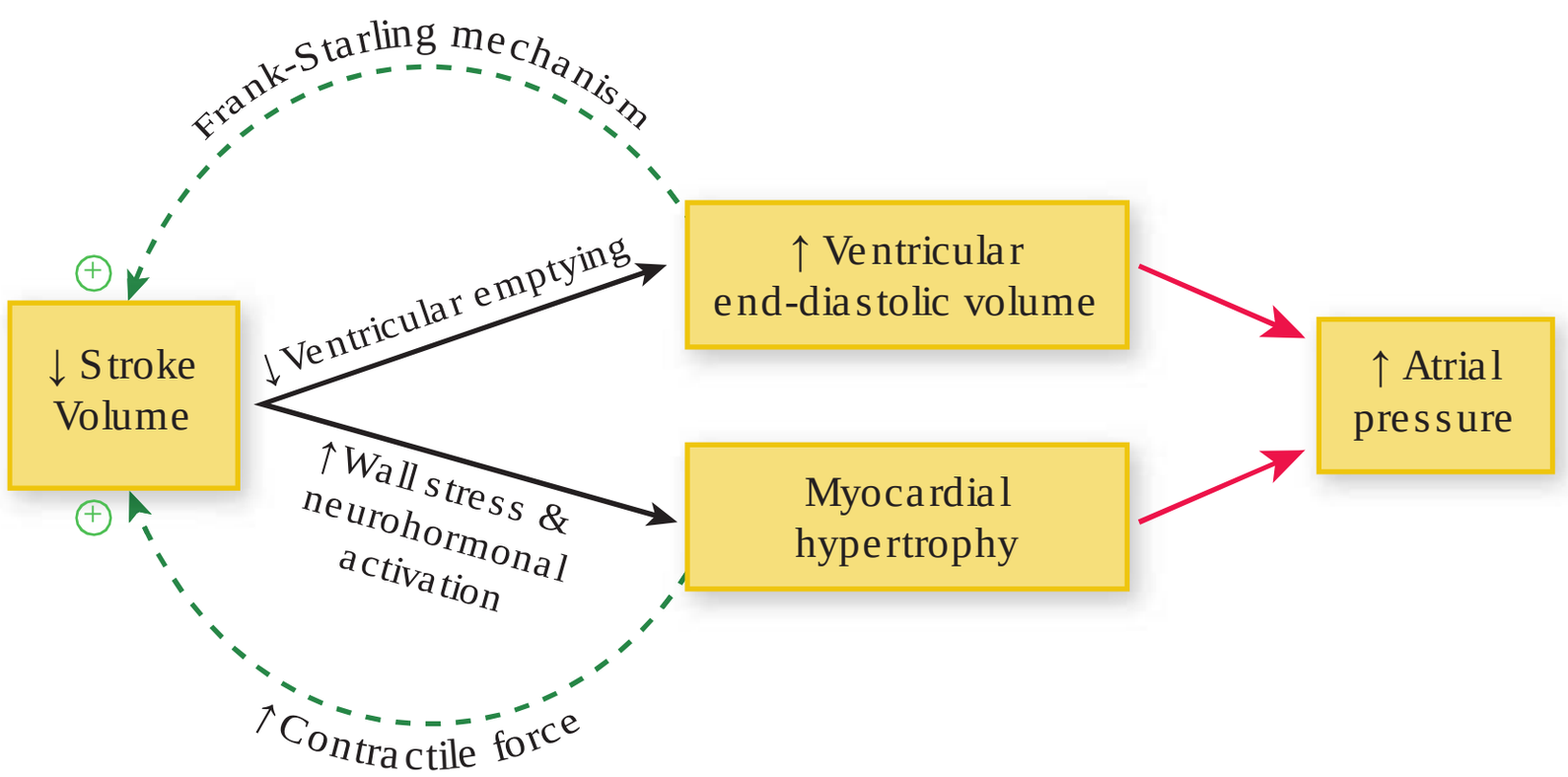

FIGURE 9-8. Compensatory mechanisms in heart failure. Both the Frank–Starling mechanism (which is invoked by the rise in ventricular end-diastolic volume) and increased contractile force (due to myocardial hypertrophy from augmented wall stress and neurohormonal activation) serve to maintain forward stroke volume (dashed green arrows). However, the chronic rise in end-diastolic volume and myocardial hypertrophy passively augment atrial pressure (red arrows), which may in turn contribute to symptoms of heart failure (e.g., pulmonary congestion in the case of left-sided heart failure).

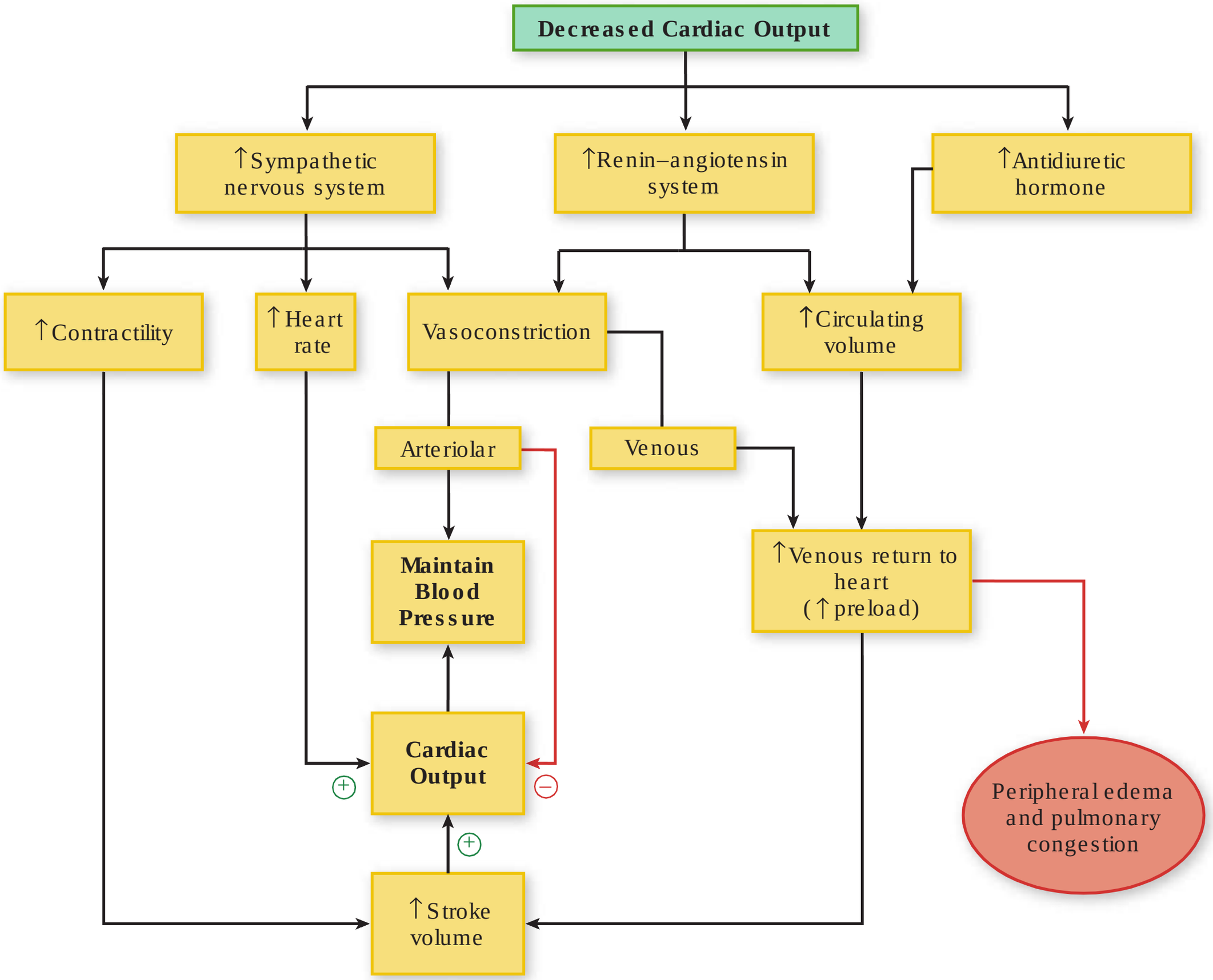

FIGURE 9-9. Compensatory neurohormonal stimulation develops in response to the reduced forward cardiac output and blood pressure of heart failure. Increased activity of the sympathetic nervous system, renin–angiotensin–aldosterone system, and antidiuretic hormone serves to support the cardiac output and blood pressure (boxes). However, adverse consequences of these activations (red lines) include an increase in afterload from excessive vasoconstriction (which may then impede cardiac output) and excess f uid retention, which contributes to peripheral edema and pulmonary congestion.

organs, even in the setting of a reduced cardiac output. That is, because blood pressure (BP) is equal to the product of cardiac output (CO) and total peripheral resistance (TPR),

$$BP = CO \times TPR$$

a rise in TPR induced by these compensatory mechanisms can nearly balance the fall in CO and, in the early stages of heart failure, maintain fairly normal BP. In addition, neurohormonal activation results in salt and water retention, which in turn increases intravascular volume and left ventricular preload, maximizing stroke volume via the Frank–Starling mechanism.

Although the acute effects of neurohormonal stimulation are compensatory and benef cial, chronic activation of these mechanisms often ultimately proves deleterious to the failing heart and contributes to a progressive downhill course, as described later.

Adrenergic Nervous System

The fall in cardiac output in heart failure is sensed by baroreceptors in the carotid sinus and aortic arch. These receptors decrease their rate of f ring in proportion to the fall in BP, and the signal is transmitted by the 9th and 10th cranial nerves to the cardiovascular control

center in the medulla. As a consequence, sympathetic outflow to the heart and peripheral circulation is enhanced, and parasympathetic tone is diminished. There are three immediate consequences (see Fig. 9-9): (1) an increase in heart rate, (2) augmentation of ventricular contractility, and (3) vasoconstriction caused by stimulation of α-receptors on the systemic veins and arteries.

The increased heart rate and ventricular contractility directly augment cardiac output (see Fig. 9-2). Vasoconstriction of the venous and arterial circulations is also initially benef cial. Venous constriction augments blood return to the heart, which increases preload and raises stroke volume through the Frank–Starling mechanism, as long as the ventricle is operating on the ascending portion of its ventricular performance curve. Arteriolar constriction increases the peripheral vascular resistance and therefore helps to maintain blood pressure (BP = CO × TPR). The regional distribution of α-receptors is such that during sympathetic stimulation, blood flow is redistributed to vital organs (e.g., heart and brain) at the expense of the skin, splanchnic viscera, and kidneys.

Renin–Angiotensin–Aldosterone System

This system is also activated early in patients with heart failure (see Fig. 9-9), mediated by increased renin release. The main stimuli for renin secretion from the juxtaglomerular cells of the kidney in heart failure patients include (1) decreased renal artery perfusion pressure secondary to low cardiac output, (2) decreased salt delivery to the macula densa of the kidney owing to alterations in intrarenal hemodynamics, and (3) direct stimulation of juxtaglomerular β-receptors by the activated adrenergic nervous system.

Renin is an enzyme that cleaves circulating angiotensinogen to form angiotensin I, which is then rapidly cleaved by endothelial cell–bound angiotensin-converting enzyme (ACE) to form angiotensin II (AII), a potent vasoconstrictor (see Chapter 13). Increased AII constricts arterioles and raises total peripheral resistance, thereby serving to maintain systemic blood pressure. In addition, AII acts to increase intravascular volume by two mechanisms: (1) at the hypothalamus, it stimulates thirst and therefore water intake, and (2) at the adrenal cortex, it acts to increase aldosterone secretion. The latter hormone promotes sodium reabsorption from the distal convoluted tubule of the kidney into the circulation (see Chapter 17), serving to augment intravascular volume. The rise in intravascular volume increases left ventricular preload and thereby augments cardiac output via the Frank–Starling mechanism in patients on the ascending portion of the ventricular performance curve (see Fig. 9-3).

Antidiuretic Hormone

Secretion of this hormone (also termed vasopressin) by the posterior pituitary is increased in many patients with heart failure, presumably mediated through arterial baroreceptors, and by increased levels of AII. ADH contributes to increased intravascular volume because it promotes water retention in the distal nephron. The increased intravascular volume serves to augment left ventricular preload and cardiac output. ADH also appears to contribute to systemic vasoconstriction.

Although each of these neurohormonal alterations in heart failure is initially benef cial, continued activation ultimately proves harmful. For example, the increased circulating volume and augmented venous return to the heart may eventually worsen engorgement of the lung vasculature, exacerbating congestive pulmonary symptoms. Furthermore, the elevated arteriolar resistance increases the afterload against which the failing left ventricle contracts and may therefore ultimately impair stroke volume and reduce cardiac output (see Fig. 9-9). In addition, the increased heart rate augments metabolic demand and can therefore further reduce the performance of the failing heart. Continuous sympathetic activation

results in down-regulation of cardiac β-adrenergic receptors and up-regulation of inhibitory G proteins, contributing to a decrease in the myocardium's sensitivity to circulating catecholamines and a reduced inotropic response.

Chronically elevated levels of AII and aldosterone have additional detrimental effects. They provoke the production of cytokines (small proteins that mediate cell–cell communication and immune responses), activate macrophages, and stimulate f broblasts, resulting in f brosis and adverse remodeling of the failing heart.

Because the undesired consequences of chronic neurohormonal activation eventually outweigh the benef ts, much of today's pharmacologic therapy of heart failure is designed to moderate these "compensatory" mechanisms, as examined later in the chapter.

Natriuretic Peptides

In contrast to the ultimately adverse consequences of the neurohormonal alterations described in the previous section, the natriuretic peptides are natural "benef cial" hormones secreted in heart failure in response to increased intracardiac pressures. The best studied of these are atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP). ANP is stored in atrial cells and is released in response to atrial distention. BNP is not detected in normal hearts but is produced when ventricular myocardium is subjected to hemodynamic stress (e.g., in heart failure or during myocardial infarction). Clinical studies have shown a close relationship between serum BNP levels and the severity of heart failure.

Actions of the natriuretic peptides are mediated by specif c natriuretic receptors and are largely opposite to those of the other hormone systems activated in heart failure. They result in excretion of sodium and water, vasodilatation, inhibition of renin secretion, and antagonism of the effects of AII on aldosterone and vasopressin levels. Although these effects are benef cial to patients with heart failure, they are usually not suff cient to fully counteract the vasoconstriction and volume-retaining effects of the other activated hormonal systems.

Other Peptides

Among other peptides that are generated in heart failure is **endothelin-1**, a potent vasoconstrictor, derived from endothelial cells lining the vasculature (see Chapter 6). In patients with heart failure, the plasma concentration of endothelin-1 correlates with disease severity and adverse outcomes. Drugs designed to inhibit endothelin receptors (and therefore blunt adverse vasoconstriction) improve LV function, but long-term clinical benef ts have not been demonstrated in heart failure patients.

Ventricular Hypertrophy and Remodeling

Ventricular hypertrophy and remodeling are important compensatory processes that develop over time in response to hemodynamic burdens. Wall stress (as def ned earlier) is often increased in developing heart failure because of either LV dilatation (increased chamber radius) or the need to generate high systolic pressures to overcome excessive afterload (e.g., in aortic stenosis or hypertension). A sustained increase in wall stress (along with neurohormonal and cytokine alterations) stimulates the development of myocardial hypertrophy and deposition of extracellular matrix. This increased mass of muscle f bers serves as a compensatory mechanism that helps to maintain contractile force and counteracts the elevated ventricular wall stress (recall that wall thickness is in the denominator of the Laplace wall stress formula). However, because of the increased stiffness of the hypertrophied wall, these benef ts come at the expense of higher-than-normal diastolic ventricular pressures, which are transmitted to the left atrium and pulmonary vasculature (see Fig. 9-8).

The pattern of compensatory hypertrophy and remodeling that develops depends on whether the ventricle is subjected to chronic volume or pressure overload. Chronic chamber dilatation owing to volume overload (e.g., chronic mitral or aortic regurgitation) results in the synthesis of new sarcomeres in series with the old, causing the myocytes to elongate. The radius of the ventricular chamber therefore enlarges, doing so in proportion to the increase in wall thickness, and is termed **eccentric hypertrophy**. Chronic pressure overload (e.g., caused by hypertension or aortic stenosis) results in the synthesis of new sarcomeres in parallel with the old (i.e., the myocytes thicken), termed **concentric hypertrophy**. In this situation, the wall thickness increases without proportional chamber dilatation, and wall stress may therefore be reduced substantially.

Such hypertrophy and remodeling help to reduce wall stress and maintain contractile force, but ultimately, ventricular function may decline further, allowing the chamber to dilate out of proportion to wall thickness. When this occurs, the excessive hemodynamic burden on the contractile units produces a downward spiral of deterioration with progressive heart failure symptomatology.

MYOCYTE LOSS AND CELLULAR DYSFUNCTION

Impairment of ventricular function in heart failure may result from the actual loss of myocytes and/or impaired function of living myocytes. The loss of myocytes may result from cellular necrosis (e.g., from myocardial infarction or exposure to cardiotoxic drugs such as doxorubicin) or apoptosis (programmed cell death). In apoptosis, genetic instructions activate intracellular pathways that cause the cell to fragment and undergo phagocytosis by other cells, without an inflammatory response. Implicated triggers of apoptosis in heart failure include elevated catecholamines, AII, inflammatory cytokines, and mechanical strain on the myocytes owing to the augmented wall stress.

Even viable myocardium in heart failure is abnormal at the ultrastructural and molecular levels. Mechanical wall stress, neurohormonal activation, and inflammatory cytokines, such as tumor necrosis factor (TNF), are believed to alter the genetic expression of contractile proteins, ion channels, catalytic enzymes, surface receptors, and secondary messengers in the myocyte. Experimental evidence has demonstrated such changes at the subcellular level that affect intracellular calcium handling by the sarcoplasmic reticulum, decrease the responsiveness of the myofilaments to calcium, impair excitation–contraction coupling, and alter cellular energy production. Cellular mechanisms currently considered the most important contributors to dysfunction in heart failure include (1) a reduced cellular ability to maintain calcium homeostasis and/or (2) changes in the production, availability, and utilization of high-energy phosphates. However, the exact subcellular alterations that result in heart failure have not yet been unraveled, and this is an active area of cardiovascular research.

PRECIPITATING FACTORS

Many patients with heart failure remain asymptomatic for extended periods either because the impairment is mild or because cardiac dysfunction is balanced by the compensatory mechanisms described earlier. Often, clinical manifestations are precipitated by circumstances that increase the cardiac workload and tip the balanced state into one of decompensation.

Common precipitating factors are listed in Table 9-3. For example, conditions of increased metabolic demand such as fever or infection may not be matched by a sufficient increase in output by the failing heart, so that symptoms of cardiac insufficiency are precipitated. Tachyarrhythmias precipitate heart failure by decreasing diastolic ventricular filling time and by increasing myocardial oxygen demand. Excessively low heart rates directly cause a drop in cardiac output (remember, cardiac output = stroke volume × heart rate). An increase in salt

TABLE 9-3 Factors That May Precipitate Symptoms in Patients with Chronic Compensated Heart Failure

Increased metabolic demands
Fever
Infection
Anemia
Tachycardia
Hyperthyroidism
Pregnancy
Increased circulating volume (increased preload)
Excessive sodium content in diet
Excessive fluid administration
Renal failure
Conditions that increase afterload
Uncontrolled hypertension
Pulmonary embolism (increased right ventricular afterload)
Conditions that impair contractility
Negative inotropic medications
Myocardial ischemia or infarction
Excessive ethanol ingestion
Failure to take prescribed heart failure medications
Excessively slow heart rate

ingestion, renal dysfunction, or failure to take prescribed diuretic medications may increase the circulating volume, thus promoting systemic and pulmonary congestion. Uncontrolled hypertension depresses systolic function because of excessive afterload. A large pulmonary embolism results in both hypoxemia (and therefore decreased myocardial oxygen supply) and augmented right ventricular afterload. Ischemic insults (i.e., myocardial ischemia or infarction), ethanol ingestion, or negative inotropic medications (e.g., large doses of β-blockers) can all depress myocardial contractility and precipitate symptoms in the otherwise compensated congestive heart failure patient.

CLINICAL MANIFESTATIONS

The clinical manifestations of heart failure result from impaired forward cardiac output and/or elevated venous pressures and relate to the ventricle that has failed (Table 9-4). A patient may present with the chronic progressive symptoms of heart failure described here or, in certain cases, with sudden decompensation of left-sided heart function (e.g., acute pulmonary edema, as described later in the chapter).

Symptoms

The most prominent manifestation of chronic left ventricular failure is dyspnea (breathlessness) on exertion. Controversy regarding the cause of this symptom has centered on whether it results primarily from pulmonary venous congestion or from decreased forward cardiac output. A pulmonary venous pressure that exceeds approximately 20 mm Hg leads to transudation of fluid into the pulmonary interstitium and congestion of the lung parenchyma. The resulting reduced pulmonary compliance increases the work of breathing to move the same volume of air. Moreover, the excess fluid in the interstitium compresses the walls of the bronchioles and alveoli, increasing the resistance to airflow and requiring greater effort

TABLE 9-4 Common Symptoms and Physical Findings in Heart Failure

Symptoms	Physical Findings
Left sided	
Dyspnea	Diaphoresis (sweating)
Orthopnea	Tachycardia, tachypnea
Paroxysmal nocturnal dyspnea	Pulmonary rales
Fatigue	Loud P_2
	S_3 gallop (in systolic dysfunction)
	S_4 gallop (in diastolic dysfunction)
Right sided	
Peripheral edema	Jugular venous distention
Right upper quadrant discomfort (because of hepatic enlargement)	Hepatomegaly
	Peripheral edema

of respiration. In addition, juxtacapillary receptors (J receptors) are stimulated and mediate rapid shallow breathing. The heart failure patient can also suffer from dyspnea even in the absence of pulmonary congestion, because reduced blood flow to overworked respiratory muscles and accumulation of lactic acid may also contribute to that sensation. Heart failure may initially cause dyspnea only on exertion, but more severe dysfunction results in symptoms at rest as well.

Other manifestations of low forward output in heart failure may include dulled mental status because of reduced cerebral perfusion and impaired urine output during the day because of decreased renal perfusion. The latter often gives way to increased urinary frequency at night (nocturia) when, while supine, blood flow is redistributed to the kidney, promoting renal perfusion and diuresis. Reduced skeletal muscle perfusion may result in fatigue and weakness.

Other congestive manifestations of heart failure include orthopnea, paroxysmal nocturnal dyspnea (PND), and nocturnal cough. Orthopnea is the sensation of labored breathing while lying flat and is relieved by sitting upright. It results from the redistribution of intravascular blood from the gravity-dependent portions of the body (abdomen and lower extremities) toward the lungs after lying down. The degree of orthopnea is generally assessed by the number of pillows on which the patient sleeps to avoid breathlessness. Sometimes, orthopnea is so signif cant that the patient may try to sleep upright in a chair.

PND is severe breathlessness that awakens the patient from sleep 2 to 3 hours after retiring to bed. This frightening symptom results from the gradual reabsorption into the circulation of lower extremity interstitial edema after lying down, with subsequent expansion of intravascular volume and increased venous return to the heart and lungs. A nocturnal cough is another symptom of pulmonary congestion and is produced by a mechanism similar to orthopnea. Hemoptysis (coughing up blood) may result from rupture of engorged bronchial veins.

In right-sided heart failure, the elevated systemic venous pressures can result in abdominal discomfort because the liver becomes engorged and its capsule stretched. Similarly, anorexia (decreased appetite) and nausea may result from edema within the gastrointestinal tract. Peripheral edema, especially in the ankles and feet, also reflects increased hydrostatic venous pressures. Because of the effects of gravity, it tends to worsen while the patient is upright during the day and is often improved by morning after lying supine at night. Even before peripheral edema develops, the patient may note an unexpected weight gain resulting from the accumulation of interstitial fluid.

TABLE 9-5 New York Heart Association Classif cation of Chronic Heart Failure

Class	Def nition
I	No limitation of physical activity
II	Slight limitation of activity. Dyspnea and fatigue with moderate exertion (e.g., walking up stairs quickly)
III	Marked limitation of activity. Dyspnea with minimal exertion (e.g., slowly walking up stairs)
IV	Severe limitation of activity. Symptoms are present even at rest.

The symptoms of heart failure are commonly graded according to the New York Heart Association (NYHA) classif cation (Table 9-5), and patients may shift from one class to another, in either direction, over time. A newer system classif es patients according to their stage in the temporal course of heart failure (Table 9-6). In this system, progression is in only one direction, from Stage A to Stage D, reflecting the typical sequence of heart failure manifestations in clinical practice.

Physical Signs

The physical signs of heart failure depend on the severity and chronicity of the condition and can be divided into those associated with left or right heart dysfunction (see Table 9-4). Patients with only mild impairment may appear well. However, a patient with severe chronic heart failure may demonstrate cachexia (a frail, wasted appearance) owing in part to poor appetite and to the metabolic demands of the increased effort in breathing. In decompensated left-sided heart failure, the patient may appear dusky (decreased cardiac output) and diaphoretic (sweating because of increased sympathetic nervous activity), and the extremities are cool because of peripheral arterial vasoconstriction. Tachypnea (rapid breathing) is common. The pattern of Cheyne–Stokes respiration may also be present in advanced heart failure, characterized by periods of hyperventilation separated by intervals of apnea (absent breathing). This pattern is related to the prolonged circulation time between the lungs and respiratory center of the brain in heart failure that interferes with the normal feedback mechanism

TABLE 9-6 Stages of Chronic Heart Failure

Stage	Description
A	The patient is at risk of developing heart failure but has not yet developed structural cardiac dysfunction (e.g., patient with coronary artery disease, hypertension, or family history of cardiomyopathy).
B	The patient with structural heart disease associated with heart failure but has not yet developed symptoms
C	The patient with current or prior symptoms of heart failure associated with structural heart disease
D	The patient with structural heart disease and refractory heart failure symptoms despite maximal medical therapy who requires advanced interventions (e.g., cardiac transplantation)

Derived from Yancy C, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure: Executive Summary A Report of the American College of Cardiology Foundation/American heart Association Task Force on Practice Guidelines. Circulation. 2013;128:1810–1852.

of systemic oxygenation. Sinus tachycardia (resulting from increased sympathetic nervous system activity) is also common. Pulsus alternans (alternating strong and weak contractions detected in the peripheral pulse) may be present as a sign of advanced ventricular dysfunction.

In left-sided heart failure, the auscultatory finding of pulmonary rales ("crackles") is created by the "popping open" of small airways during inspiration that had been closed off by edema fluid. This finding is initially apparent at the lung bases, where hydrostatic forces are greatest; however, more severe pulmonary congestion is associated with additional rales higher in the lung fields. Compression of conduction airways by pulmonary congestion may produce coarse rhonchi and wheezing; the latter finding in heart failure is termed cardiac asthma.

Depending on the cause of heart failure, palpation of the heart may show that the left ventricular impulse is not focal but diffuse (in dilated cardiomyopathy), sustained (in pressure overload states such as aortic stenosis or hypertension), or lifting in quality (in volume overload states such as mitral regurgitation). Because elevated left heart filling pressures result in increased pulmonary vascular pressures, the pulmonic component of the second heart sound is often louder than normal. An early diastolic sound (S_3) is frequently heard in adults with systolic heart failure and is caused by abnormal filling of the dilated chamber (see Chapter 2). A late diastolic sound (S_4) results from forceful atrial contraction into a stiffened ventricle and is common in states of decreased LV compliance (diastolic dysfunction). The murmur of mitral regurgitation is sometimes auscultated in left-sided heart failure if LV dilatation has stretched the valve annulus and spread the papillary muscles apart from one another, thus preventing proper closure of the mitral leaflets in systole.

In right-sided heart failure, different physical findings may be present. Cardiac examination may reveal a palpable parasternal right ventricular heave, representing RV enlargement, or a right-sided S_3 or S_4 gallop. The murmur of tricuspid regurgitation may be auscultated and is due to right ventricular enlargement, analogous to mitral regurgitation that develops in patients with LV dilatation. The elevated systemic venous pressure produced by right heart failure is manifested by distention of the jugular veins as well as hepatic enlargement with abdominal right upper quadrant tenderness. Edema accumulates in the dependent portions of the body, beginning in the ankles and feet of ambulatory patients and in the presacral regions of those who are bedridden.

Pleural effusions may develop in either left- or right-sided heart failure, because the pleural veins drain into both the systemic and pulmonary venous beds. The presence of pleural effusions is suggested on physical examination by dullness to percussion over the posterior lung bases.

Diagnostic Studies

A normal mean left atrial (LA) pressure is ≤10 mm Hg (see Fig. 3-13). If the LA pressure exceeds approximately 15 mm Hg, the chest radiograph shows upper-zone vascular redistribution, such that the vessels supplying the upper lobes of the lung are larger than those supplying the lower lobes (see Fig. 3-5). This is explained as follows: when a patient is in the upright position, blood flow is normally greater to the lung bases than to the apices because of the effect of gravity. Redistribution of flow occurs with the development of interstitial and perivascular edema, because such edema is most prominent at the lung bases (where the hydrostatic pressure is the highest), such that the blood vessels in the bases are compressed, whereas flow into the upper lung zones is less affected.

When the LA pressure surpasses 20 mm Hg, interstitial edema is usually manifested on the chest radiograph as indistinctness of the vessels and the presence of Kerley B lines (short linear markings at the periphery of the lower lung fields indicating interlobular edema—see Fig. 3-5C). If the LA pressure exceeds 25 to 30 mm Hg, alveolar pulmonary edema may develop, with opacification of the air spaces. The relationship between LA pressure and chest

radiograph f ndings is modif ed in patients with chronic heart failure because of enhanced lymphatic drainage, such that higher pressures can be accommodated with fewer radiologic signs.

Depending on the cause of heart failure, the chest radiograph may show cardiomegaly, def ned as a cardiothoracic ratio greater than 0.5 on the posteroanterior image. A high right atrial pressure also causes enlargement of the azygous vein silhouette. Pleural effusions may be present.

Assays for BNP, described earlier in the chapter, correlate well with the degree of LV dysfunction and prognosis. Furthermore, an elevated serum level of BNP can help distinguish heart failure from other causes of dyspnea, such as pulmonary parenchymal diseases.

The cause of heart failure is often evident from the history, such as a patient who has sustained a large myocardial infarction, or by physical examination, as in a patient with a murmur of valvular heart disease. When the cause is not clear from clinical evaluation, the f rst step is to determine whether systolic ventricular function is normal or depressed (see Fig. 9-6). Of the several noninvasive tests that can help make this determination, echocardiography is especially useful and readily available.

PROGNOSIS

The prognosis of heart failure is dismal in the absence of a correctable underlying cause. The 5-year mortality rate following the diagnosis ranges between 45% and 60%, with men having worse outcomes than women. Patients with severe symptoms (i.e., NYHA class III or IV) fare the least well, having a 1-year survival rate of only 40%. The greatest mortality is due to refractory heart failure, but many patients die suddenly, presumably because of associated ventricular arrhythmias. Heart failure patients with preserved EF have similar rates of hospitalization, in-hospital complications, and mortality as those with reduced EF.

Ventricular dysfunction usually begins with an inciting insult, but is a progressive process, contributed to by the maladaptive activation of neurohormones, cytokines, and continuous ventricular remodeling. Thus, it should not be surprising that measures of neurohormonal and cytokine stimulation predict survival in heart failure patients. For example, adverse prognosis correlates with the serum norepinephrine level (marker of sympathetic nervous system activity), serum sodium (reduced level reflects activation of renin–angiotensin–aldosterone system and alterations in intrarenal hemodynamics), endothelin-1, BNP, and TNF levels.

Despite the generally bleak prognosis, a heart failure patient's outlook can be substantially improved by specif c interventions, as discussed in the following sections.

TREATMENT OF HEART FAILURE WITH REDUCED EJECTION FRACTION

There are f ve main goals of therapy in patients with chronic heart failure and a reduced EF:

1. Identif cation and correction *of* the underlying condition causing heart *f*ailure. In some patients, this may require surgical repair or replacement of dysfunctional cardiac valves, coronary artery revascularization, aggressive treatment of hypertension, or cessation of alcohol consumption.
2. Elimination *of* the acute precipitating cause *of* symptoms in a patient with heart failure who was previously in a compensated state. This may include, for example, treating acute infections or arrhythmias, removing sources of excessive salt intake, or eliminating drugs that can aggravate symptomatology (e.g., certain calcium channel blockers, which have a negative inotropic effect, or nonsteroidal anti-inflammatory drugs, which can contribute to volume retention).
3. Management of heart failure symptoms:
   a. Treatment *of* pulmonary and systemic vascular congestion. This is most readily accomplished by dietary sodium restriction and diuretic medications.
   b. Measures to increase *f*orward cardiac output and perfusion of vital organs through the use of vasodilators and positive inotropic drugs.

4. Modulation of the neurohormonal response to prevent adverse ventricular remodeling in order to slow the progression of LV dysfunction.
5. Prolongation of long-term survival. There is strong evidence from clinical trials that longevity is enhanced by specif c therapies, as described below.

Diuretics

The mechanisms of action of diuretic drugs are summarized in Chapter 17. By promoting the elimination of sodium and water through the kidney, diuretics reduce intravascular volume and thus venous return to the heart. As a result, the preload of the left ventricle is decreased, and its diastolic pressure falls out of the range that promotes pulmonary congestion (Fig. 9-10, point b). The intent is to reduce the EDP (and therefore hydrostatic forces contributing to pulmonary congestion) without a signif cant fall in stroke volume. The judicious use of diuretics does not signif cantly reduce stroke volume and cardiac output in this setting, because the failing ventricle is operating on the "flat" portion of a depressed Frank–Starling curve. However, overly vigorous diuresis can lower LV f lling pressures into the steep portion of the ventricular performance curve, resulting in an undesired fall in cardiac output (see Fig. 9-10, point b′). Thus, diuretics should be used only if there is evidence of pulmonary congestion (rales) or peripheral interstitial fluid accumulation (edema).

Agents that act primarily at the renal loop of Henle (e.g., furosemide, torsemide, and bumetanide) are the most potent diuretics in heart failure. Thiazide diuretics (e.g.,

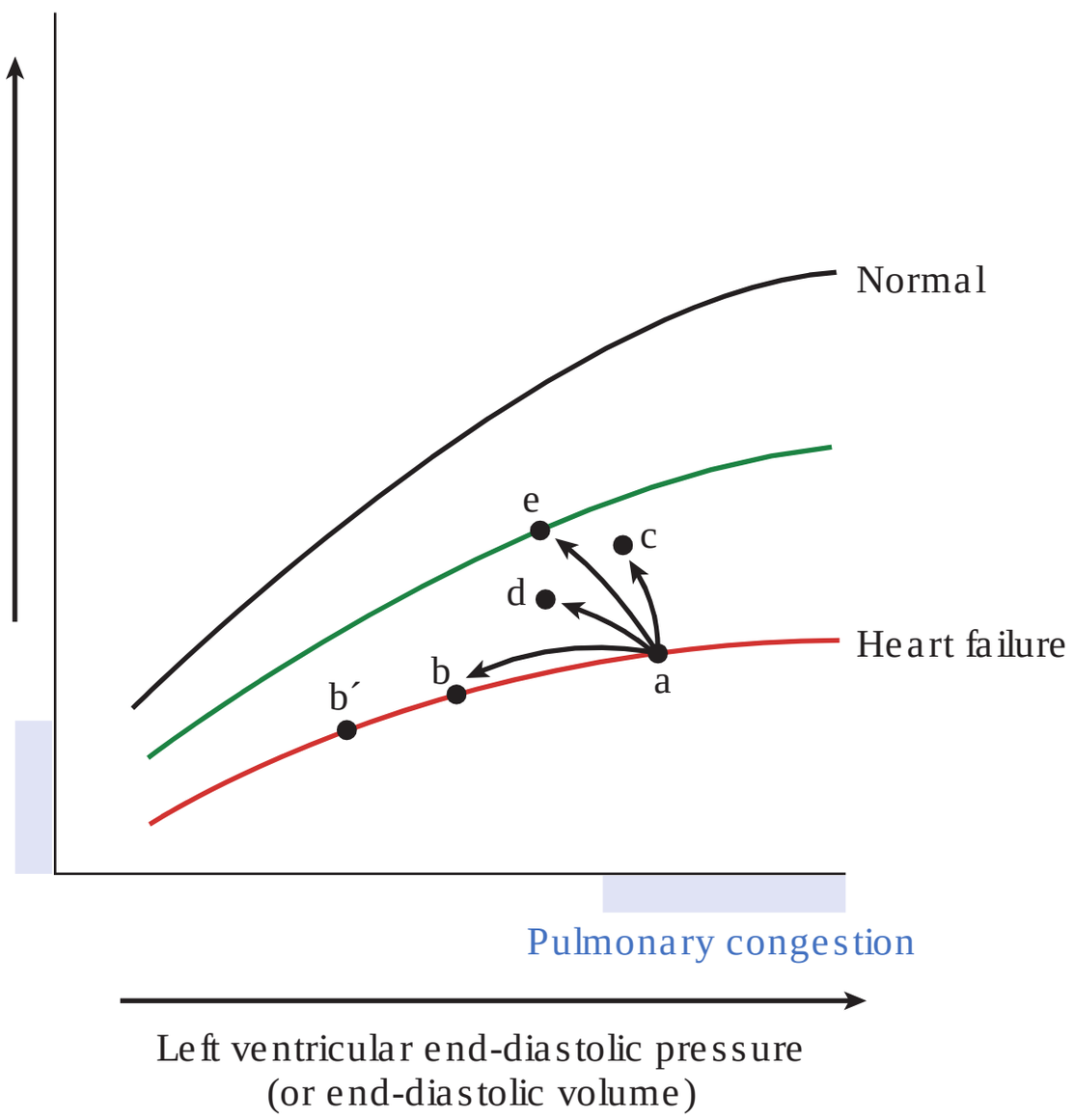

FIGURE 9-10. The effect of treatment on the left ventricular (LV) Frank–Starling curve in patients who have heart failure with reduced EF. Point a represents the failing heart on a curve that is shifted downward compared with normal. The stroke volume is reduced (with blood pressure bordering on hypotension), and the LV end-diastolic pressure (LVEDP) is increased, resulting in symptoms of pulmonary congestion. Therapy with a diuretic or pure venous vasodilator (point b on the same Frank–Starling curve) reduces LV pressure without much change in stroke volume (SV). However, excessive diuresis or venous vasodilatation may result in an undesired fall in SV with hypotension (point b′). Inotropic drug therapy (point c) and arteriolar (or "balanced") vasodilator therapy (point d) augment SV, and because of improved LV emptying during contraction, the LVEDP lessens. Point e represents the potential added benef t of combining an inotrope and vasodilator together. The middle curve shows one example of how the Frank–Starling relationship shifts upward during inotropic/vasodilator therapy but does not achieve the level of a normal ventricle.

hydrochlorothiazide and metolazone) are also useful but are less effective in the setting of decreased renal perfusion, which is often present in this condition.

The potential adverse effects of diuretics are described in Chapter 17. The most important in heart failure patients include overly vigorous diuresis resulting in a fall in cardiac output and electrolyte disturbances (particularly hypokalemia and hypomagnesemia), which may contribute to arrhythmias. In patients with acute heart failure exacerbations, diuretics should be administered intravenously (either by bolus injections or continuous infusion) because venous congestion can limit the absorption of oral diuretics from the gut.

Vasodilators

One of the most important cardiac advances in the late twentieth century was the introduction of vasodilator therapy for the treatment of heart failure, particularly ACE inhibitors. As indicated earlier, neurohormonal compensatory mechanisms in heart failure often lead to excessive vasoconstriction, volume retention, and ventricular remodeling, with progressive deterioration of cardiac function. Vasodilator drugs help to reverse these adverse consequences. Moreover, multiple studies have shown that certain vasodilator regimens signif cantly extend survival in patients with heart failure. The pharmacology of these drugs is described in Chapter 17.

Venous vasodilators (e.g., nitrates) increase venous capacitance and thereby decrease venous return to the heart and left ventricular preload. Consequently, LV diastolic pressures fall and the pulmonary capillary hydrostatic pressure declines, similar to the hemodynamic effects of diuretic therapy. As a result, pulmonary congestion improves, and as long as the heart failure patient is on the relatively "flat" part of the depressed Frank–Starling curve (see Fig. 9-10), the cardiac output does not fall despite the reduction in ventricular f lling pressure. However, venous vasodilatation in a patient who is operating on the steeper part of the curve may result in an undesired fall in stroke volume, cardiac output, and blood pressure.

Pure arteriolar vasodilators (e.g., hydralazine) reduce systemic vascular resistance and therefore LV afterload, which in turn permits increased ventricular muscle f ber shortening during systole (see Fig. 9-5B). This results in an augmented stroke volume and is represented on the Frank–Starling diagram as a shift in an upward direction (see Fig. 9-10, point d). Although an arterial vasodilator might be expected to reduce blood pressure—an undesired effect in patients with heart failure who may already be hypotensive—this generally does not happen. As resistance is reduced by arteriolar vasodilatation, a concurrent rise in cardiac output usually occurs, such that blood pressure remains constant or decreases only mildly.

Some groups of drugs result in vasodilatation of both the venous and arteriolar circuits ("balanced" vasodilators). Of these, the most important are agents that inhibit the renin–angiotensin–aldosterone system. **ACE inhibitors** (described in Chapters 13 and 17) interrupt the production of AII, thereby modulating the vasoconstriction incited by that hormone in heart failure patients. In addition, because aldosterone levels fall in response to ACE inhibitor therapy, sodium elimination is facilitated, resulting in reduced intravascular volume and improvement of systemic and pulmonary vascular congestion. ACE inhibitors also augment circulating levels of bradykinin (see Chapter 17), which is thought to contribute to benef cial vasodilatation in heart failure. As a result of these effects, ACE inhibitors limit maladaptive ventricular remodeling in patients with chronic heart failure and following acute myocardial infarction (see Chapter 7).

Supporting the benef cial hemodynamic and neurohormonal blocking effects of ACE inhibitors, many large clinical trials have shown that these drugs reduce heart failure symptoms, reduce the need for hospitalization, and most importantly, extend survival in patients with heart failure with reduced EF. Thus, ACE inhibitors are standard f rst-line chronic therapy for patients with LV systolic dysfunction.

The renin–angiotensin–aldosterone system can also be therapeutically inhibited by **angiotensin II receptor blockers (ARBs)**, as described in Chapters 13 and 17. Since AII can be

formed by pathways other than ACE, ARBs provide a more complete inhibition of the system than ACE inhibitors, through blockade of the actual AII receptor (see Fig. 17.6). Conversely, ARBs do not cause the potentially benef cial rise in serum bradykinin. The net result is that the hemodynamic effects and mortality benef t of ARBs in heart failure are similar to those of ACE inhibitors. Thus, they are prescribed to heart failure patients mainly when ACE inhibitors are not tolerated (e.g., because of bradykinin-mediated side effects such as cough or angioedema).

Chronic therapy using the combination of the venous dilator **isosorbide dinitrate** plus the arteriolar dilator **hydralazine** has also been shown to improve survival in patients with moderate symptoms of heart failure. However, when the ACE inhibitor enalapril was compared with the hydralazine–isosorbide dinitrate (H-ISDN) combination, the ACE inhibitor was shown to produce the greater improvement in survival. Thus, H-ISDN is generally substituted when a patient cannot tolerate ACE inhibitor or ARB therapy (e.g., because of renal insuff ciency or hyperkalemia). Of note, the African American Heart Failure trial demonstrated that the addition of H-ISDN to standard heart failure therapy (including a diuretic, β-blocker, and ACE inhibitor or ARB) in black patients with heart failure further improved functional status and survival.

Nesiritide (human recombinant BNP) is an intravenous vasodilator drug available for hospitalized patients with decompensated heart failure. It causes rapid and potent vasodilatation, reduces elevated intracardiac pressures, and augments forward cardiac output. However, it is an expensive drug that does not improve outcomes and may worsen renal function, so its use should be restricted to patients who have not responded to, or cannot tolerate, other intravenous vasodilators, such as intravenous nitroglycerin or nitroprusside (see Chapter 17).

Positive Inotropic Drugs

Inotropic drugs include β-adrenergic agonists, digitalis glycosides, and phosphodiesterase type 3 inhibitors (see Chapter 17). By increasing the availability of intracellular calcium, each of these drug groups enhances the force of ventricular contraction and therefore shifts the Frank–Starling curve in an upward direction (see Fig. 9-10). As a result, stroke volume and cardiac output are augmented at any given ventricular EDV. Therefore, these agents may be useful in treating patients with systolic dysfunction, but typically not those with heart failure with preserved EF.

β-Adrenergic agonists (e.g., dobutamine and dopamine) are administered intravenously for temporary hemodynamic support in acutely ill, hospitalized patients. Their long-term use is limited by the lack of an oral form of administration and by the development of drug tolerance. The latter refers to the progressive decline in effectiveness during continued administration of the drug, possibly owing to down-regulation of myocardial adrenergic receptors. Likewise, the role of **phosphodiesterase 3 inhibitors** (e.g., milrinone) is limited to the intravenous treatment of congestive heart failure in acutely ill patients. Despite the initial promise of effective oral phosphodiesterase 3 inhibitors, studies thus far actually demonstrate reduced survival among patients receiving this form of treatment.

One of the oldest forms of inotropic therapy is **digitalis** (see Chapter 17), which can be administered intravenously or orally. Digitalis preparations enhance contractility, reduce cardiac enlargement, improve symptoms, and augment cardiac output in patients with systolic heart failure. Digitalis also increases the sensitivity of the baroreceptors, so that the compensatory sympathetic drive in heart failure is blunted, a desired effect that reduces left ventricular afterload. By slowing AV nodal conduction and thereby reducing the rate of ventricular contractions, digitalis has an added benef t in patients with congestive heart failure who have concurrent atrial f brillation. Although digitalis can improve symptomatology and reduce the rate of hospitalizations in heart failure patients, it has not been shown to improve long-term survival. Thus, its use is limited to patients who remain symptomatic despite other standard therapies or to help slow the ventricular rate if atrial f brillation is also present. Digitalis is not useful in the treatment of heart failure with preserved EF because it does not improve ventricular relaxation properties.

β-Blockers

Historically, β-blockers were thought to be contraindicated in patients with systolic dysfunction because their negative inotropic effect would be expected to worsen symptomatology. However, clinical trials have actually shown that long-term β-blocker therapy has important benefits in patients with stable chronic heart failure with reduced EF, including augmented cardiac output, reduced hemodynamic deterioration, the need for fewer hospitalizations, and improved survival. The explanation for these desired effects remains conjectural but may relate to the drugs' effects on reducing heart rate and blunting chronic sympathetic activation or to their anti-ischemic properties.

The three β-blockers that have been shown to be beneficial in randomized clinical trials of heart failure include **carvedilol** (a nonselective β-blocker with weak α-blocking properties—see Chapter 17) and the β_1-selective agents **metoprolol succinate** and **bisoprolol**. These drugs are well tolerated in stable patients (i.e., those without recent deterioration of heart failure symptoms or active volume overload). Nonetheless, β-blockers should always be used cautiously in heart failure to prevent acute deterioration related to their negative inotropic effect. Regimens should be started at low dosage and augmented gradually.

Aldosterone Antagonist Therapy

There is evidence that chronic excess of aldosterone in heart failure contributes to cardiac fibrosis and adverse ventricular remodeling. Antagonists of this hormone (which have been used historically as mild diuretics—see Chapter 17) have shown clinical benefit in heart failure patients. For example, in a clinical trial of patients with advanced heart failure (i.e., NYHA Class III to IV) who were already taking an ACE inhibitor and diuretics, the aldosterone receptor antagonist **spironolactone** substantially reduced mortality rates and improved heart failure symptoms. **Eplerenone**, a more specific aldosterone receptor inhibitor, has been shown to improve survival of patients with congestive heart failure after acute myocardial infarction (see Chapter 7) as well as patients with more mild forms of chronic heart failure (i.e., NYHA Class II to III). Although aldosterone antagonists have been well tolerated in carefully controlled studies, the serum potassium level must be monitored to prevent hyperkalemia, especially if there is renal impairment or concomitant ACE inhibitor therapy.

In summary, standard therapy of chronic heart failure with reduced EF should include several drugs, the cornerstones of which are an ACE inhibitor and a β-blocker. An accepted sequence of therapy is to start with an ACE inhibitor as well as a diuretic if pulmonary or systemic congestive symptoms are present. If the patient is unable to tolerate the ACE inhibitor, then an ARB (or hydralazine plus isosorbide dinitrate) may be substituted. For patients without recent clinical deterioration or volume overload, a β-blocker should be added. Those with persistent symptomatic heart failure may benefit from the addition of an aldosterone antagonist. For refractory symptoms, digoxin can be prescribed for its hemodynamic benefit.

Additional Therapies

Arrhythmia Management

Atrial and ventricular arrhythmias frequently accompany chronic heart failure. For example, atrial fibrillation is very common in this setting and conversion back to sinus rhythm (see Chapter 11) can substantially improve cardiac output. Ventricular arrhythmias are also frequent in heart failure and may lead to sudden death. The antiarrhythmic drug that is most effective at suppressing arrhythmias and least likely to provoke other dangerous rhythm disorders in heart failure patients is amiodarone. However, studies of amiodarone

for the treatment of asymptomatic ventricular arrhythmias in heart failure have not shown a consistent survival benef t. In addition, heart failure patients with symptomatic or sustained ventricular arrhythmias, or those with inducible ventricular tachycardia during electrophysiologic testing, benef t more from the insertion of an implantable cardioverter–def brillator (ICD; see Chapter 11). Based on the results of large-scale randomized trials, ICD implantation is indicated for many patients with heart failure and at least moderately reduced systolic function (e.g., LVEF ≤35%), regardless of the presence of ventricular arrhythmias, because this approach reduces the likelihood of sudden cardiac death in this population.

Cardiac Resynchronization Therapy

Intraventricular conduction abnormalities with widened QRS complexes (especially left bundle branch block) are common in patients with advanced heart failure. Such abnormalities can actually contribute to cardiac symptoms because of the resultant uncoordinated pattern of right and left ventricular contraction. Advanced pacemakers have been developed that stimulate both ventricles simultaneously, thus resynchronizing the contractile effort. This technique of biventricular pacing, also termed cardiac resynchronization therapy (CRT), has been shown to augment left ventricular systolic function, improve exercise capacity, and reduce the frequency of heart failure exacerbations and mortality. Thus, CRT is appropriate for selected patients with advanced systolic dysfunction (LV EF ≤35%), a prolonged QRS duration (> 120 ms) and continued symptoms of heart failure despite appropriate pharmacologic therapies. Since patients who receive CRT are typically also candidates for an ICD, modern devices combine both functions in a single, small implantable unit.

Cardiac Mechanical Circulatory Support and Replacement Therapy

A patient with severe LV dysfunction whose condition remains refractory to maximal medical management may be a candidate for cardiac transplantation. However, only approximately 4,000 transplants are performed worldwide each year because of a shortage of donor hearts, many fewer than the number of patients with refractory heart failure symptoms. For certain patients who are too ill to wait for a heart donor, or who are not eligible for a transplant, alternative mechanical therapies are in selected use. Ventricular assist devices (VADs) and implantable total artif cial hearts can be used to support cardiac pump function in such patients. Recent technological advances in continuous-flow left-sided VADs have resulted in 1-year survival rates greater than 70%, compared to less than 25% survival rates in similar groups of advanced heart failure patients treated with medical therapy alone.

TREATMENT OF HEART FAILURE WITH PRESERVED EJECTION FRACTION

The goals of therapy in heart failure with preserved EF include (1) the relief of pulmonary and systemic congestion and (2) addressing correctable causes of the impaired diastolic function (e.g., hypertension, coronary artery disease). Diuretics reduce pulmonary congestion and peripheral edema but must be used cautiously to avoid under f lling of the left ventricle. A stiffened left ventricle relies on higher-than-normal pressures to achieve adequate diastolic f lling (see Fig. 9-7B), and excessive diuresis could reduce f lling and therefore impair stroke volume and cardiac output (see Fig. 9-10, point b′).

Unlike patients with impaired systolic function, β-blockers, ACE inhibitors, and ARBs have no demonstrated mortality benef t in patients with heart failure with preserved EF. The aldosterone antagonist spironolactone was recently shown to reduce the frequency of hospitalizations for heart failure in this population, but did not improve the survival rate. Since contractile function is preserved, inotropic drugs have no therapeutic role in this syndrome.

ACUTE HEART FAILURE

In contrast to the findings of chronic heart failure described to this point, patients with acute heart failure are those who present with urgent and often life-threatening symptomatology. Acute heart failure may develop in a previously asymptomatic patient (e.g., resulting from an acute coronary syndrome [Chapter 7], severe hypertension [Chapter 13], or acute valvular regurgitation [Chapter 8]), or it may complicate chronic compensated heart failure following a precipitating trigger (see Table 9-3). Management of acute heart failure typically requires hospitalization and prompt interventions.

The classification of patients with acute heart failure, and the approach to therapy, can be tailored based on the presence or absence of two major findings at the bedside: (1) volume overload (i.e., "wet" vs. "dry") as a reflection of elevated LV filling pressures and (2) signs of decreased cardiac output with reduced tissue perfusion ("cold" vs. "warm" extremities). Examples of a "wet" profile, indicative of volume overload, include pulmonary rales, jugular venous distension, and edema of the lower extremities. Figure 9-11 shows how patients with acute heart failure can be divided into four profiles based on observations of these parameters.

Profile A indicates normal hemodynamics. Cardiopulmonary symptoms in such patients would be due to factors other than heart failure, such as parenchymal lung disease or transient myocardial ischemia. Profiles B and C are typical of patients with acute pulmonary edema (described below). Those with Profile B have "wet" lungs but preserved ("warm") tissue perfusion. Profile C is more serious; in addition to congestive findings, impaired forward cardiac output results in marked systemic vasoconstriction (e.g., activation of the sympathetic nervous system) and therefore "cold" extremities. Patients with Profile C have a prognosis worse than those with Profile B, who in turn have poorer outcomes than those with Profile A.

Patients with Profile L do not represent an extension of this continuum. Rather, they display "cold" extremities due to low output (hence the label "L") but no signs of vascular congestion. This profile may arise in patients who are actually volume deplete, or those with very limited cardiac reserve in the absence of volume overload (e.g., a patient with a dilated left ventricle and mitral regurgitation who becomes short of breath with activity because of the inability to generate adequate forward cardiac output). These profiles of acute heart failure should not be confused with the classification of chronic heart failure (Stages A through D) presented in Table 9-6.

The goals of therapy in acute heart failure are to (1) normalize ventricular filling pressures and (2) restore adequate tissue perfusion. Identification of the patient's profile type guides therapeutic interventions. For example, a patient with Profile B would require diuretic and/or vasodilator therapy for pulmonary edema (described in the next section), and those with Profile C may additionally require intravenous inotropic medications to strengthen cardiac output. Patients with Profile L may require volume expansion. The presence of profile A would prompt a search for contributions to the patient's symptoms other than heart failure.

↑LV filling Pressures
(Pulmonary and/or Systemic Congestion)

	No	**Yes**
No	Profile A "Warm and Dry"	Profile B "Warm and Wet"
Yes	Profile L "Cold and Dry"	Profile C "Cold and Wet"

FIGURE 9-11. Hemodynamic profiles in acute heart failure. (Derived from Nohria A, Tsang SW, Fang JC, et al. Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure. J Am Coll Cardiol. 2003;41:1797–1804.)

Acute Pulmonary Edema

A common manifestation of acute left-sided heart failure (e.g., typical of Profiles B and C) is cardiogenic pulmonary edema, in which elevated capillary hydrostatic

pressure causes rapid accumulation of fluid within the interstitium and alveolar spaces of the lung. In the presence of normal plasma oncotic pressure, pulmonary edema develops when the pulmonary capillary wedge pressure, which reflects LV diastolic pressure, exceeds approximately 25 mm Hg.

This condition is frequently accompanied by hypoxemia because of shunting of pulmonary blood flow through regions of hypoventilated alveoli. Like other manifestations of acute heart failure, pulmonary edema may appear suddenly in a previously asymptomatic person (e.g., in the setting of an acute myocardial infarction) or in a patient with chronic compensated congestive heart failure following a precipitating event (see Table 9-3). Pulmonary edema is a horrifying experience for the patient, resulting in severe dyspnea and anxiety while struggling to breathe.

On examination, the patient is tachycardic and may demonstrate cold, clammy skin owing to peripheral vasoconstriction in response to increased sympathetic outflow (i.e., Prof le C). Tachypnea and coughing of "frothy" sputum represent transudation of fluid into the alveoli. Rales are present initially at the bases and later throughout the lung f elds, sometimes accompanied by wheezing because of edema within the conductance airways.

Pulmonary edema is a life-threatening emergency that requires immediate improvement of systemic oxygenation and elimination of the underlying cause. The patient should be seated upright to permit pooling of blood within the systemic veins of the lower body, thereby reducing venous return to the heart. Supplemental oxygen is provided by a face mask. Morphine sulfate is administered intravenously to reduce anxiety and also acts as a venous dilator to facilitate pooling of blood peripherally. A rapidly acting diuretic, such as intravenous furosemide, is administered to further reduce LV preload and pulmonary capillary hydrostatic pressure. Other means of reducing preload include administration of nitrates (often intravenously). Intravenous inotropic drugs (e.g., dopamine) may increase forward CO and are used primarily in patients with Prof le C. During resolution of the pulmonary congestion and hypoxemia, attention should be directed at identifying and treating the underlying precipitating cause.

An easy-to-remember mnemonic for the principal components of management of pulmonary edema is the alphabetic sequence LMNOP:

Lasix (trade name for furosemide)
Morphine
Nitrates
Oxygen
Position (sit upright)

SUMMARY

- Ventricular stroke volume (SV) is a function of preload, afterload, and contractility; SV rises when there is an increase in preload, a decrease in afterload, or augmented contractility.
- Cardiac output = heart rate × stroke volume.
- Ventricular EDV (or EDP) represents preload and is influenced by the chamber's compliance.
- Ventricular ESV depends on the afterload and contractility but not on the preload.
- Heart failure is a clinical syndrome in which cardiac output (CO) fails to meet the metabolic demands of the body or meets those demands only if cardiac f lling pressures are abnormally high.
- Chronic heart failure may be classif ed into two categories: (1) heart failure with reduced EF owing to impaired left ventricular systolic function and (2) heart failure with preserved EF (e.g., diastolic dysfunction).
- Compensatory mechanisms in heart failure that initially maintain circulatory function include (1) preload augmentation with increased stroke volume via the Frank–Starling

mechanism, (2) activation of neurohormonal systems, and (3) ventricular hypertrophy; however, these compensations eventually become maladaptive, contributing to adverse ventricular remodeling and progressive deterioration of ventricular function.

- Symptoms of heart failure may be exacerbated by precipitating factors that increase metabolic demand (e.g., tachycardia), increase circulating volume, augment afterload, or decrease contractility.
- Treatment of heart failure includes addressing the underlying cause of the condition, eliminating precipitating factors, and modulating detrimental neurohormonal activations.
- Standard therapy of symptomatic heart failure with reduced EF includes an ACE inhibitor, β-blocker, and sometimes an aldosterone antagonist; for patients who do not tolerate an ACE inhibitor, an AII receptor blocker or the combination of hydralazine plus nitrates can be substituted.
- Diuretics should be used to treat volume overload, and inotropic drugs are typically reserved for acute "rescue" management of low CO states.
- For patients with heart failure with reduced EF who meet specif c criteria, an implantable cardioverter–def brillator and/or cardiac resynchronization therapy (biventricular pacing) may be indicated.
- For refractory end-stage heart failure, cardiac transplantation and/or mechanical circulatory support should be considered in carefully selected patients.
- Therapy for heart failure with preserved EF relies primarily on diuretics to relieve pulmonary congestion, but such therapy must be administered cautiously to avoid excess reduction of preload and hypotension.
- Acute heart failure can be prof led by, and treatment decisions based on, the presence or absence of (1) elevated left heart f lling pressures (wet vs. dry) and (2) reduced systemic tissue perfusion with elevated systemic vascular resistance (i.e., cold vs. warm).

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