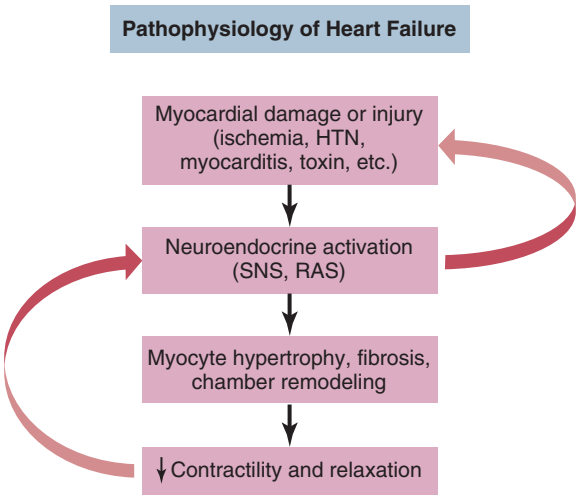

FIGURE 5-3 The diagram illustrates the progressive nature of left ventricular dysfunction that can follow an initial cardiac insult. Attenuation of the neurohumoral activation (or blockade of the downstream effects) may interrupt the positive feedback and slow or reverse the progression of heart failure. HTN, Hypertension; RAS, renin-angiotensin system; SNS, sympathetic nervous system.

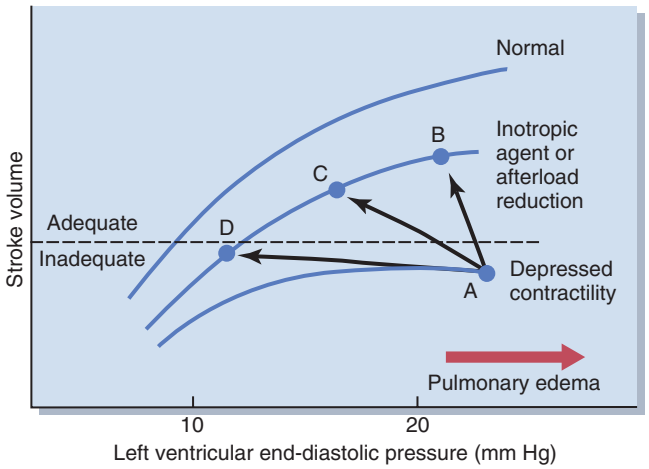

FIGURE 5-4 Normal and abnormal ventricular function curves. When the left ventricular end-diastolic pressure acutely rises above 20 mm Hg (point A), pulmonary edema often occurs. The effect of diuresis or venodilation is to move leftward along the same curve, with a resultant improvement in pulmonary congestion and with minimal decrease in cardiac output. The stroke volume is poor at any point along this depressed contractility curve; therapeutic maneuvers to raise it more toward the normal curve are necessary to improve cardiac output significantly. Unlike the effect of diuretics, the effect of vasodilator therapy in a patient with heart failure is to move the patient into another ventricular function curve intermediately between the normal and depressed curves. When the patient's ventricular function moves from point A to B by the administration of one of these agents, the LVEDP may also decrease because of improved cardiac function. Further administration of diuretics or venodilators may shift the patient further to the left along the same curve from point B to C and eliminate the risk for pulmonary edema. A vasodilating agent that has arteriolar and venous dilating properties (e.g., nitroprusside) would shift this patient directly from point A to C. If this agent shifts the patient from point A to D because of excessive venodilation or administration of diuretics, the cardiac output may fall too low, even though the LVEDP would be normal (10 mm Hg) for a normal heart. LVEDPs between 15 and 18 mm Hg are usually optimal in the failing heart to maximize cardiac output but avoid pulmonary edema. (Modified from the Heart Failure Society of America: Questions about heart failure. Available at http://www.abouthf.org/questions_stages.htm. Accessed August 2, 2014.)

differences between the hydrostatic pressure in the pulmonary capillaries and the oncotic pressure of the lungs. Depressed myocardial contractility (in HFrEF) and increased chamber stiffness (in HFpEF) can lead to pulmonary congestion through this same mechanism.

After the initial compensatory mechanism, the failing heart undergoes ventricular remodeling, characterized by myocardial structural and functional abnormalities resulting in a dilated, spherical ventricle with reduced contractility. Ventricular remodeling occurs in response to pressure and volume overload, myocyte loss, or a combination of these factors, resulting in progressive decline in contractility. Ventricular remodeling begins with ventricular hypertrophy in response to increased wall stress to decrease myocardial oxygen consumption. If the extent of hypertrophy is inadequate to normalize wall stress, a vicious cycle is established.

The remodeling changes occur to make the failing ventricle more efficient and can be understood in the context of LaPlace's law ($T = P \times r/w_t$), where T = tension, P = pressure, r = the radius of the chamber or vessel, and W_t = the thickness of the wall. As tension (force) increases, pressure increases proportionally. Untreated, this mechanism leads to progressive ventricular dilation and chamber enlargement, causing increased wall stress, increased myocardial oxygen consumption, and progressively worsening contractility.

Neurohormonal Activation

Activation of the sympathetic nervous system is the first response to decreased cardiac output. It results in the release of epinephrine and norepinephrine, which bind all adrenergic receptors. This results in stimulation or inhibition of G proteins (i.e., G_s and G_i subtypes). G protein activation upregulates adenylate cyclase, which converts adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP). cAMP signals protein kinase A, which phosphorylates ryanodine receptors, leading to increased intracellular calcium levels, which increase contractility by phosphorylating and inhibiting phospholamban. Stimulation of the sympathetic nervous system also increases ventricular relaxation (i.e., lusitropy) and increases the basal heart rate. These effects, although beneficial initially, are ultimately detrimental to the myocardium.

The RAAS is stimulated by the sympathetic nervous system and by decreased blood flow to the afferent arteriole of the nephron, resulting in the release of renin. This ultimately leads to activation of angiotensin II, which is a potent vasoconstrictor, with the initial response to supply adequate blood to vital organs. However, angiotensin II increases afterload, wall stress, and myocardial oxygen consumption and leads to a decrease in stroke volume. Angiotensin II also leads to sympathetic nervous system activation, aldosterone release, and myocardial fibrosis, perpetuating the cycle.

The release of aldosterone prompts sodium reabsorption, promoting water retention to effectively maintain cardiac output. Aldosterone also has fibrotic properties. The release of vasopressin promotes free water absorption by the kidney. These changes are responsible for many of the clinical signs and symptoms associated with HF.