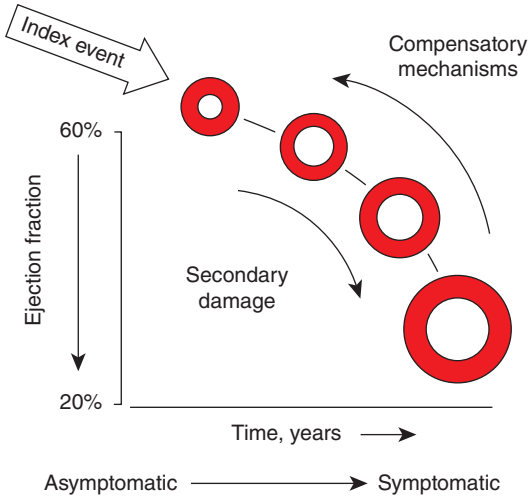

FIGURE 279-1 Pathogenesis of heart failure with a depressed ejection fraction. Heart failure begins after an index event produces an initial decline in the heart's pumping capacity. After this initial decline in pumping capacity, a variety of compensatory mechanisms are activated, including the adrenergic nervous system, the renin-angiotensin-aldosterone system, and the cytokine system. In the short term, these systems are able to restore cardiovascular function to a normal homeostatic range with the result that the patient remains asymptomatic. However, with time, the sustained activation of these systems can lead to secondary end-organ damage within the ventricle, with worsening left ventricular remodeling and subsequent cardiac decompensation. *(From D Mann: Circulation 100:999, 1999.)*

to sustain and modulate LV function for a period of months to years. The compensatory mechanisms that have been described thus far include (1) activation of the renin-angiotensin-aldosterone (RAA) and adrenergic nervous systems, which are responsible, respectively, for maintaining cardiac output through increased retention of salt and water (Fig. 279-2), and (2) increased myocardial contractility. In addition, there is activation of a family of countervailing vasodilatory molecules, including the atrial and brain natriuretic peptides (ANP and BNP), prostaglandins (PGE_2 and PGI_2), and nitric oxide (NO), that offsets the excessive peripheral vascular vasoconstriction. Genetic background, sex, age, or environment may influence these compensatory mechanisms, which are able to modulate LV function within a physiologic/homeostatic range so that the functional capacity of the patient is preserved or is depressed only minimally. Thus, patients may remain asymptomatic or minimally symptomatic for a period of years; however, at some point patients become overtly symptomatic, with a resultant striking increase in morbidity and mortality rates. Although the exact mechanisms that are responsible for this transition are not known, as will be discussed below, the transition to symptomatic HF is accompanied by increasing activation of neurohormonal, adrenergic, and cytokine systems that lead to a series of adaptive changes within the myocardium collectively referred to as *LV remodeling*.

In contrast to our understanding of the pathogenesis of HF with a depressed EF, our understanding of the mechanisms that contribute to the development of HF with a preserved EF is still evolving. That is, although diastolic dysfunction (see below) was thought to be the only mechanism responsible for the development of HF with a preserved EF, community-based studies suggest that additional extracardiac mechanisms may be important, such as increased vascular stiffness and impaired renal function.

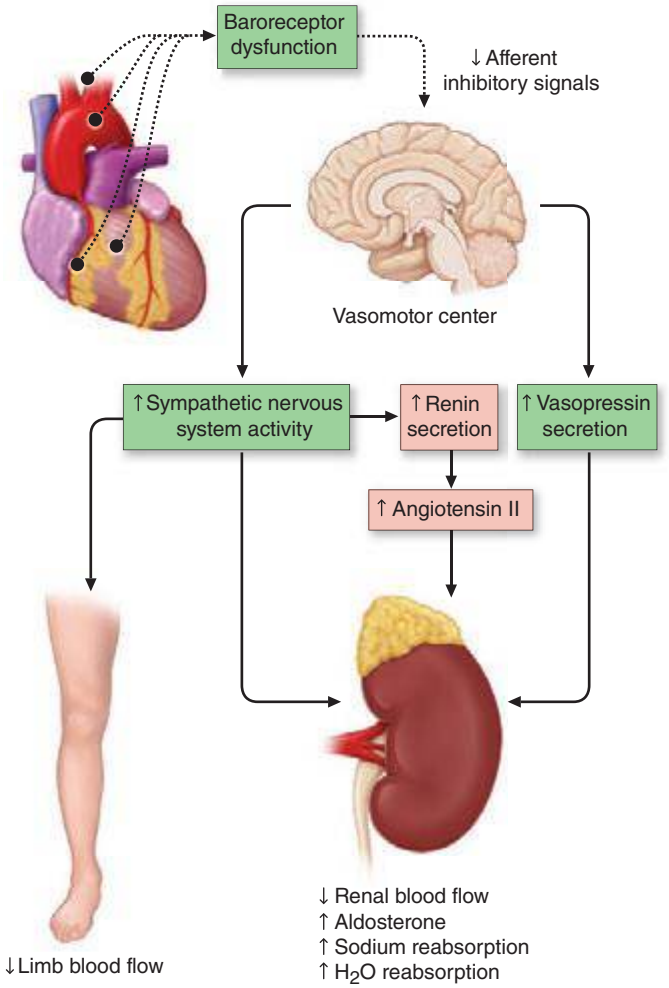

FIGURE 279-2 Activation of neurohormonal systems in heart failure. The decreased cardiac output in heart failure (HF) patients results in an "unloading" of high-pressure baroreceptors (*circles*) in the left ventricle, carotid sinus, and aortic arch. This unloading of the peripheral baroreceptors leads to a loss of inhibitory parasympathetic tone to the central nervous system (CNS), with a resultant generalized increase in efferent sympathetic tone, and nonosmotic release of arginine vasopressin (AVP) from the pituitary. AVP (or antidiuretic hormone [ADH]) is a powerful vasoconstrictor that increases the permeability of the renal collecting ducts, leading to the reabsorption of free water. These afferent signals to the CNS also activate efferent sympathetic nervous system pathways that innervate the heart, kidney, peripheral vasculature, and skeletal muscles.

Sympathetic stimulation of the kidney leads to the release of renin, with a resultant increase in the circulating levels of angiotensin II and aldosterone. The activation of the renin-angiotensin-aldosterone system promotes salt and water retention and leads to vasoconstriction of the peripheral vasculature, myocyte hypertrophy, myocyte cell death, and myocardial fibrosis. Although these neurohormonal mechanisms facilitate short-term adaptation by maintaining blood pressure, and hence perfusion to vital organs, the same neurohormonal mechanisms are believed to contribute to end-organ changes in the heart and the circulation and to the excessive salt and water retention in advanced HF. *(Modified from A Nohria et al: Neurohormonal, renal and vascular adjustments, in Atlas of Heart Failure: Cardiac Function and Dysfunction, 4th ed, WS Colucci [ed]. Philadelphia, Current Medicine Group 2002, p. 104.)*

BASIC MECHANISMS OF HEART FAILURE

Heart Failure with a Reduced Ejection Fraction LV remodeling develops in response to a series of complex events that occur at the cellular and molecular levels (Table 279-3). These changes include (1) myocyte hypertrophy; (2) alterations in the contractile properties of the myocyte; (3) progressive loss of myocytes through necrosis, apoptosis, and autophagic cell death; (4) β-adrenergic desensitization; (5) abnormal myocardial energetics and metabolism; and (6) reorganization of the extracellular matrix with dissolution of the organized structural collagen weave surrounding myocytes and subsequent replacement by an interstitial collagen matrix that does not