TABLE 279-3 OVERVIEW OF LEFT VENTRICULAR REMODELING

Alterations in Myocyte Biology
Excitation-contraction coupling
Myosin heavy chain (fetal) gene expression
β-Adrenergic desensitization
Hypertrophy
Myocytolysis
Cytoskeletal proteins
Myocardial Changes
Myocyte loss
Necrosis
Apoptosis
Autophagy
Alterations in extracellular matrix
Matrix degradation
Myocardial fibrosis
Alterations in Left Ventricular Chamber Geometry
Left ventricular (LV) dilation
Increased LV sphericity
LV wall thinning
Mitral valve incompetence

Source: Adapted from D. Mann: Pathophysiology of heart failure, in *Braunwald's Heart Disease,* 8th ed, PL Libby et al (eds). Philadelphia, Elsevier, 2008, p. 550.

provide structural support to the myocytes. The biologic stimuli for these profound changes include mechanical stretch of the myocyte, circulating neurohormones (e.g., norepinephrine, angiotensin II), inflammatory cytokines (e.g., tumor necrosis factor [TNF]), other peptides and growth factors (e.g., endothelin), and reactive oxygen species (e.g., superoxide). The sustained overexpression of these biologically active molecules is believed to contribute to the progression of HF by virtue of the deleterious effects they exert on the heart and the circulation. Indeed, this insight forms the clinical rationale for using pharmacologic agents that antagonize these systems (e.g., angiotensin-converting enzyme [ACE] inhibitors and beta blockers) in treating patients with HF **(Chap. 280)**.

To understand how the changes that occur in the failing cardiac myocyte contribute to depressed LV systolic function in HF, it is instructive first to review the biology of the cardiac muscle cell **(Chap. 265e)**. Sustained neurohormonal activation and mechanical overload result in transcriptional and posttranscriptional changes in the genes and proteins that regulate excitation-contraction coupling and cross-bridge interaction **(see Figs. 265e-6 and 265e-7)**. The changes that regulate excitation-contraction include decreased function of sarcoplasmic reticulum Ca^{2+} adenosine triphosphatase (SERCA2A), resulting in decreased calcium uptake into the sarcoplasmic reticulum (SR), and hyperphosphorylation of the ryanodine receptor, leading to calcium leakage from the SR. The changes that occur in the cross-bridges include decreased expression of α-myosin heavy chain and increased expression of β-myosin heavy chain, myocytolysis, and disruption of the cytoskeletal links between the sarcomeres and the extracellular matrix. Collectively, these changes impair the ability of the myocyte to contract and therefore contribute to the depressed LV systolic function observed in patients with HF.

Myocardial relaxation is an adenosine triphosphate (ATP)-dependent process that is regulated by uptake of cytoplasmic calcium into the SR by SERCA2A and extrusion of calcium by sarcolemmal pumps **(see Fig. 265e-7)**. Accordingly, reductions in ATP concentration, as occurs in ischemia, may interfere with these processes and lead to slowed myocardial relaxation. Alternatively, if LV filling is delayed because LV compliance is reduced (e.g., from hypertrophy or fibrosis), LV filling pressures will similarly remain elevated at end diastole **(see Fig. 265e-11)**. An increase in heart rate disproportionately shortens the time for diastolic filling, which may lead to elevated LV filling pressures, particularly in noncompliant ventricles. Elevated LV end-diastolic filling pressures result in increases in pulmonary capillary pressures, which can contribute to the dyspnea experienced by patients with diastolic dysfunction. In addition to impaired myocardial relaxation, increased myocardial stiffness secondary to cardiac hypertrophy and increased myocardial collagen content may contribute to diastolic failure. Importantly, diastolic dysfunction can occur alone or in combination with systolic dysfunction in patients with HF.

Left Ventricular Remodeling *Ventricular remodeling* refers to the changes in LV mass, volume, and shape and the composition of the heart that occur after cardiac injury and/or abnormal hemodynamic loading conditions. LV remodeling may contribute independently to the progression of HF by virtue of the mechanical burdens that are engendered by the changes in the geometry of the remodeled LV. In addition to the increase in LV end-diastolic volume, LV wall thinning occurs as the left ventricle begins to dilate. The increase in wall thinning, along with the increase in afterload created by LV dilation, leads to a functional *afterload mismatch* that may contribute further to a decrease in stroke volume. Moreover, the high end-diastolic wall stress might be expected to lead to (1) hypoperfusion of the subendocardium, with resultant worsening of LV function; (2) increased oxidative stress, with the resultant activation of families of genes that are sensitive to free radical generation (e.g., TNF and interleukin 1β); and (3) sustained expression of stretch-activated genes (angiotensin II, endothelin, and TNF) and/or stretch activation of hypertrophic signaling pathways. Increasing LV dilation also results in tethering of the papillary muscles with resulting incompetence of the mitral valve apparatus and functional mitral regurgitation, which in turn leads to further hemodynamic overloading of the ventricle. Taken together, the mechanical burdens that are engendered by LV remodeling contribute to the progression of HF. Recent studies have shown that LV remodeling can be reversed following medical and device therapy and that reverse LV remodeling is associated with improved clinical outcomes in patients with HFrEF. Indeed, one of the goals of therapy for HF is to prevent and/or reverse LV remodeling.

CLINICAL MANIFESTATIONS

Symptoms The cardinal symptoms of HF are fatigue and shortness of breath. Although fatigue traditionally has been ascribed to the low cardiac output in HF, it is likely that skeletal-muscle abnormalities and other noncardiac comorbidities (e.g., anemia) also contribute to this symptom. In the early stages of HF, dyspnea is observed only during exertion; however, as the disease progresses, dyspnea occurs with less strenuous activity, and it ultimately may occur even at rest. The origin of dyspnea in HF is probably multifactorial **(Chap. 47e)**. The most important mechanism is pulmonary congestion with accumulation of interstitial or intra-alveolar fluid, which activates juxtacapillary J receptors, which in turn stimulate the rapid, shallow breathing characteristic of cardiac dyspnea. Other factors that contribute to dyspnea on exertion include reductions in pulmonary compliance, increased airway resistance, respiratory muscle and/or diaphragm fatigue, and anemia. Dyspnea may become less frequent with the onset of right ventricular (RV) failure and tricuspid regurgitation.

ORTHOPNEA Orthopnea, which is defined as dyspnea occurring in the recumbent position, is usually a later manifestation of HF than is exertional dyspnea. It results from redistribution of fluid from the splanchnic circulation and lower extremities into the central circulation during recumbency, with a resultant increase in pulmonary capillary pressure. Nocturnal cough is a common manifestation of this process and a frequently overlooked symptom of HF. Orthopnea generally is relieved by sitting upright or sleeping with additional pillows. Although orthopnea is a relatively specific symptom of HF, it may occur in patients with abdominal obesity or ascites and patients with pulmonary disease whose lung mechanics favor an upright posture.

PAROXYSMAL NOCTURNAL DYSPNEA (PND) This term refers to acute episodes of severe shortness of breath and coughing that generally occur at night and awaken the patient from sleep, usually 1–3 h after the