- *Frank-Starling mechanism*, in which increased filling volumes dilate the heart and thereby increase subsequent actin-myosin cross-bridge formation, enhancing contractility and stroke volume
- *Myocardial adaptations, including hypertrophy with or without cardiac chamber dilation.* In many pathologic states, heart failure is preceded by cardiac hypertrophy, the compensatory response of the myocardium to increased mechanical work. The collective molecular, cellular, and structural changes that occur as a response to injury or changes in loading conditions are called *ventricular remodeling.*
- *Activation of neurohumoral* systems to augment heart function and/or regulate filling volumes and pressures
  - Release of norepinephrine by adrenergic cardiac nerves of the autonomic nervous system (which increases heart rate and augments myocardial contractility and vascular resistance)
  - Activation of the renin-angiotensin-aldosterone system
  - Release of atrial natriuretic peptide. The latter two factors act to adjust filling volumes and pressures.

These adaptive mechanisms may be adequate to maintain normal cardiac output in the face of acute perturbations, but their capacity to do so may ultimately be overwhelmed. Moreover, superimposed pathologic changes, such as myocyte apoptosis, intracellular cytoskeletal alterations, and extracellular matrix deposition, may cause further structural and functional disturbances. Heart failure can result from progressive deterioration of myocardial contractile function *(systolic dysfunction)*—reflected as a decrease in ejection fraction (EF, the percentage of blood volume ejected from the ventricle during systole; normal is approximately 45% to 65%). Reduction in EF can occur with ischemic injury, inadequate adaptation to pressure or volume overload due to hypertension or valvular disease, or ventricular dilation. Increasingly, heart failure is recognized as resulting from an inability of the heart chamber to expand and fill sufficiently during diastole *(diastolic dysfunction)*, for example, due to left ventricular hypertrophy, myocardial fibrosis, constrictive pericarditis, or amyloid deposition.

## Cardiac Hypertrophy: Pathophysiology and Progression to Heart Failure

**Sustained increase in mechanical work due to pressure or volume overload (e.g., systemic hypertension or aortic stenosis) or trophic signals (e.g., those mediated through the activation of β-adrenergic receptors) cause myocytes to increase in size *(hypertrophy)*; cumulatively, this increases the size and weight of the heart** (Fig. 12-1). Hypertrophy requires increased protein synthesis, thus enabling the assembly of additional sarcomeres, as well as increasing the numbers of mitochondria. Hypertrophic myocytes also have enlarged nuclei, attributable to increased DNA ploidy resulting from DNA replication in the absence of cell division. The pattern of hypertrophy reflects the nature of the stimulus. In *pressure-overload hypertrophy* (e.g., due to hypertension or aortic stenosis), new sarcomeres are predominantly assembled in parallel to the long axes of cells, expanding the cross-sectional area of myocytes in ventricles and causing a concentric increase in wall thickness. In contrast, *volume-overload hypertrophy* is characterized by new sarcomeres being assembled in series within existing sarcomeres, leading primarily to ventricular dilation. As a result, in dilation due to volume overload, or dilation that accompanies failure of a previously pressure overloaded heart, the wall thickness may be increased, normal, or less than normal. Consequently, heart weight, rather than wall thickness, is the best measure of hypertrophy in dilated hearts.

Cardiac hypertrophy can be substantial in clinical heart disease. Heart weights of two to three times normal are common in patients with systemic hypertension, ischemic heart disease, aortic stenosis, mitral regurgitation, or dilated cardiomyopathy, and heart weights can be three- to four-fold greater than normal in those with aortic regurgitation or hypertrophic cardiomyopathy.

Important changes at the tissue and cell level occur with cardiac hypertrophy. Importantly, myocyte hypertrophy is not accompanied by a proportional increase in capillary numbers. As a result, the supply of oxygen and nutrients to the hypertrophied heart, particularly one undergoing pressure overload hypertrophy, is more tenuous than in the normal heart. At the same time, oxygen consumption by the hypertrophied heart is elevated due to the increased workload that drives the process. Hypertrophy is also often accompanied by deposition of fibrous tissue (interstitial fibrosis). Molecular changes include the expression of immediate-early genes (e.g., *FOS, JUN, MYC,* and *EGR1*) (Chapter 2). With prolonged hemodynamic overload, there may be a shift to a gene expression pattern resembling that seen during fetal cardiac development (including selective expression of embryonic/fetal forms of β-myosin heavy chain, natriuretic peptides, and collagen).

At a functional level, cardiac hypertrophy is associated with heightened metabolic demands due to increases in mass, heart rate, and contractility (inotropic state, or force of contraction), all of which increase cardiac oxygen consumption. *As a result of these changes, the hypertrophied heart is vulnerable to ischemia-related decompensation,* which can evolve to cardiac failure and eventually lead to death.

The proposed sequence of initially beneficial—and later harmful—events in response to increased cardiac work is summarized in Figure 12-2. *The molecular and cellular changes in hypertrophied hearts that initially mediate enhanced function may themselves contribute to the development of heart failure.* This can occur through:

- Abnormal myocardial metabolism
- Alterations of intracellular handling of calcium ions
- Myocyte apoptosis
- Reprogramming of gene expression, which may occur in part through changes in expression of miRNAs, small noncoding RNAs that inhibit gene expression (Chapter 1).

The degree of structural abnormality of the heart in CHF does not always reflect the severity of dysfunction, and the structural, biochemical, and molecular basis for myocardial contractile failure can be obscure.