wall thickness is usually 0.3 to 0.5 cm, while the left ventricle wall is 1.3 to 1.5 cm thick. Increases in heart weight or ventricular thickness above these normal limits indicates *hypertrophy*, and an enlarged chamber size implies *dilation*; both can represent compensatory changes in response to heart disease and to volume and/or pressure overloads (see later). Increased cardiac weight or size (or both)—resulting from hypertrophy and/or dilation—is called *cardiomegaly*.

## Myocardium

The pumping function of the heart is accomplished via the coordinated contraction (during *systole*) and relaxation (during *diastole*) of the cardiac myocytes that comprise the *myocardium*. Left ventricular myocytes are arranged circumferentially in a spiral orientation that helps to generate a coordinated wave of contraction that spreads from the apex to the base of the heart. In contrast, right ventricular myocytes have a somewhat less structured organization. The contractile apparatus within myocytes is organized into a series of subunits called *sarcomeres*, composed of highly ordered networks of thick filaments (primarily *myosin* in the center of the sarcomere) interlaced with thin filaments (largely *actin,* attached to the end of the sarcomere) and regulatory proteins such as troponin and tropomyosin. The actin and myosin filaments partially overlap with each other, giving rise to the striated appearance of cardiac myocytes (overlapping areas of actin and myosin are dark while the intervening areas are light).

Contraction results as myosin filaments ratchet adjacent actin filaments toward the center—shortening individual sarcomeres, and collectively leading to myocyte shortening. The amount of force generated is determined by the distance each sarcomere contracts. Thus, moderate ventricular dilation during diastole creates a greater distance over which the sarcomere can subsequently shorten and augment the force of systolic contraction. This compensatory mechanism serves to accommodate differing volume and pressure demands. Unfortunately, there is an upper limit to the benefit of increased stretching during diastole. With excessive dilation, the overlap of the actin and myosin filaments is reduced and the force of contraction decreases sharply, leading to heart failure.

Atrial myocytes are relatively haphazardly arranged, and thus generate weaker contractile forces than the ventricles. Some atrial cells have distinctive cytoplasmic electron-dense storage granules that contain *atrial natriuretic peptide*; this is a peptide hormone that promotes arterial vasodilation and stimulates renal salt and water elimination (*natriuresis* and *diuresis*), actions that are beneficial in the setting of hypertension and congestive heart failure.

The coordinated beating of cardiac myocytes depends on *intercalated discs*—specialized intercellular junctions that facilitate cell-to-cell mechanical and electrical (ionic) coupling. Within the intercalated discs (and at the lateral borders of adjacent myocytes), *gap junctions* facilitate synchronized waves of myocyte contraction by permitting rapid movement of ions (e.g., sodium, potassium, calcium) between adjoining cells. Abnormalities in the spatial distribution of gap junctions in a variety of heart diseases can cause electromechanical dysfunction (*arrhythmia*) and/or heart failure.

## Valves

The four cardiac valves—tricuspid, pulmonary, mitral, and aortic—maintain unidirectional blood flow. Valve function depends on the mobility, pliability, and structural integrity of the *leaflets* of the *atrioventricular* valves (tricuspid and mitral) or *cusps* of the *semilunar valves* (aortic and pulmonary). Cardiac valves are lined by endothelium and share a similar, tri-layered architecture:

- A dense collagenous core (*fibrosa*) at the outflow surface and connected to the valvular supporting structures
- A central core of loose connective tissue (*spongiosa*)
- A layer rich in elastin (*ventricularis* or *atrialis* depending on which chamber it faces) on the inflow surface

The collagen of the ventricularis is largely responsible for the mechanical integrity of a valve, while the elastic tissue of the atrialis/ventricularis imparts a rapid recoil to achieve prompt valve closure. The proteoglycan-rich spongiosa facilitates the interactions of the collagenous (relatively stiff) and elastic layers during the cardiac cycle. Crucial to function are the valvular interstitial cells, the most abundant cell type in the heart valves, and distributed throughout all of its layers. Valvular interstitial cells synthesize extracellular matrix (ECM) and express matrix degrading enzymes (including matrix metalloproteinases [MMPs], along with inhibitors that remodel collagen and other matrix components. Valvular interstitial cells comprise a diverse and dynamic population of resident cells that can alter their phenotypes and functions in response to changing hemodynamic stresses.

The function of the semilunar valves depends on the integrity and coordinated movements of the cuspal attachments. Thus, dilation of the aortic root can hinder coaptation of the aortic valve cusps during closure and result in valvular regurgitation. In contrast, the competence of the atrioventricular valves depends on the proper function not only the leaflets but also the tendinous cords and the attached papillary muscles of the ventricular wall. Left ventricular dilation, a ruptured tendinous cord, or papillary muscle dysfunction can all interfere with valve closure, causing valvular insufficiency.

Because they are thin enough to be nourished by diffusion from the blood, normal leaflets and cusps have only scant blood vessels limited to the proximal portion. **Pathologic changes of valves are largely of three types: damage to collagen that weakens the leaflets, exemplified by mitral valve prolapse; nodular calcification beginning in interstitial cells, as in calcific aortic stenosis; and fibrotic thickening, the key feature in rheumatic heart disease** (see later).

## Conduction System

Coordinated contraction of the cardiac muscle depends on propagation of electrical impulses—accomplished through specialized excitatory and conducting myocytes within the cardiac conduction system that regulate heart rate and rhythm. The frequency of electrical impulses that course through the conduction system is sensitive to neural inputs (e.g., vagal stimulation), extrinsic adrenergic agents (e.g., adrenaline), hypoxia, and potassium concentration (i.e., hyperkalemia can block signal transmission