altogether). Inputs from the autonomic nervous system can increase the heart rate to twice normal within seconds, and are important for physiologic responses to exercise or other states associated with increased oxygen demand.

The components of the conduction system include:

- *Sinoatrial (SA) node* pacemaker (at the junction of the right atrial appendage and superior vena cava)
- *Atrioventricular (AV) node* (located in the right atrium along the atrial septum)
- *Bundle of His*, connecting the right atrium to the ventricular septum
- Subsequent divisions into the right and left bundle branches that stimulate their respective ventricles via further arborization into the *Purkinje network*

The cells of the cardiac conduction system depolarize spontaneously, enabling them to function as cardiac pacemakers. Because the normal rate of spontaneous depolarization in the SA node (60 to 100 beats/minute) is faster than the other components, it normally sets the pace. The AV node has a gatekeeper function; by delaying the transmission of signals from the atria to the ventricles, it ensures that atrial contraction precedes ventricular systole.

Blood Supply

Cardiac myocytes rely almost exclusively on oxidative phosphorylation for their energy needs. Besides a high density of mitochondria (20% to 30% of myocyte volume), myocardial energy generation also requires a constant supply of oxygenated blood—rendering myocardium extremely vulnerable to ischemia. Nutrients and oxygen are delivered via the *coronary arteries*, with takeoffs immediately distal to the aortic valve. These initially course along the external surface of the heart *(epicardial coronary arteries)* and then penetrate the myocardium *(intramural arteries),* subsequently branching into arterioles, and eventually forming a rich arborizing vascular network so that each myocyte contacts roughly three capillaries.

There are three major epicardial coronary arteries (so-called because they form a crown or *corona* at the base of the heart):

- Left anterior descending (LAD) and left circumflex (LCX) arteries arise from the left (main) coronary artery
- Right coronary artery

The divisions of the LAD are called *diagonal* branches, and those of the LCX are *marginal branches.* The right and left coronary arteries function as end arteries, although anatomically most hearts have numerous intercoronary anastomoses (connections called collateral circulation). Blood flow to the myocardium occurs during ventricular diastole, following closure of the aortic valve, and when the microcirculation is not compressed by cardiac contraction. At rest, diastole comprises approximately two thirds of the cardiac cycle; with tachycardia (increased heart rate), the relative duration of diastole also shortens, thus potentially compromising cardiac perfusion.

Cardiac Stem Cells

Although cardiac regeneration in metazoans (e.g., newts and zebrafish) is well described, the myocardium of higher order animals is classically depicted as a permanent cell population without replicative potential. However, increasing evidence points to the presence of bone marrow–derived precursors—as well as a small population of stem cells within the myocardium—that are capable of repopulating the mammalian heart. Besides self-renewal, these cardiac stem cells generate all cell lineages seen within the myocardium. They constitute up to 5% to 10% of normal atrial cellularity, but represent only roughly 1 in 100,000 cells in a normal ventricle.

Cardiac stem cells have a very slow rate of proliferation, which is greatest in neonates, and decreases with age. The human adult heart replaces roughly 1% of its total population each year, so that by the age of 50 years, almost 45% of the total cardiomyocytes have been renewed. While stem cell numbers and progeny increase after myocardial injury or hypertrophy, albeit to a limited extent, hearts that suffer myocardial cell loss (e.g., due to infarction) do not recover any significant function in the necrotic zone (one of several features that distinguish humans from fish and newts). Nevertheless, the potential for stimulating proliferation and differentiation of these cells in vivo is tantalizing since it could facilitate recovery of myocardial function following irreversible myocardial damage. Similarly, ex vivo expansion and subsequent administration of stem cells is another strategy being explored in the unfulfilled quest to heal a broken heart. Until then a trip to the local jewelry store will have to suffice!

Effects of Aging on the Heart

The prevalence of most forms of heart disease increases with each advancing decade. Consequently, as the average population in developed countries ages, changes in the cardiovascular system that accrue with aging become increasingly significant (Table 12-1).

Epicardial fat increases, while the detritus of years of intracellular catabolism and oxidant stress accumulate in the form of intracellular lipofuscin. *Basophilic degeneration*, a gray-blue byproduct of glycogen metabolism within cardiac myocytes, is also increased. The size of the left ventricular cavity, particularly in the base-to-apex dimension, is reduced; this volume change is exacerbated by systemic hypertension and bulging of the basal ventricular septum into the left ventricular outflow tract (termed *sigmoid septum*).

Valvular aging changes include calcification of the mitral annulus and aortic valve, the latter frequently leading to aortic stenosis. In addition, the valves can develop fibrous thickening, and the mitral leaflets tend to buckle back toward the left atrium during ventricular systole, simulating a prolapsing (myxomatous) mitral valve. As this happens, increasing volume and pressure overloads lead to left atrial dilation, and with it, an increased incidence of atrial arrhythmias (e.g., fibrillation). With time, small filiform processes *(Lambl excrescences)* form on the closure lines of aortic and mitral valves, probably resulting from the organization of small thrombi.

The aorta becomes progressively stiffer, owing to the fragmentation and loss of elastic tissue and increased collagen deposition, along with the accumulation of atherosclerotic plaque. The result is less elasticity, and increased

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