

is a constituent of all lipoproteins except low-density lipoproteins. As a result, apoE^{-/-} mice exhibit high levels of cholesterol (>500mg/dL) on a normal diet, and cholesterol levels increase by a factor of four when they are fed a Western diet (high fat). Importantly, these mice also begin to develop fatty streaks in blood vessels as early as 10 weeks of age. The atherosclerotic lesions progress in a manner consistent with the development of atherosclerotic plaques in humans. The impact of potential therapeutic entities on the progression of atherosclerotic plaques can be assessed in the apoE^{-/-} mouse model by direct inspection of the plaque structure, rather than depending on circulating cholesterol levels as a surrogate maker for disease progression.³²

Models of Atrial Fibrillation

Although not generally life threatening, atrial fibrillation (AF) patients are at a substantially higher risk of heart failure, ischemia, morbidity, and mortality. The condition is characterized by an asynchronous contraction

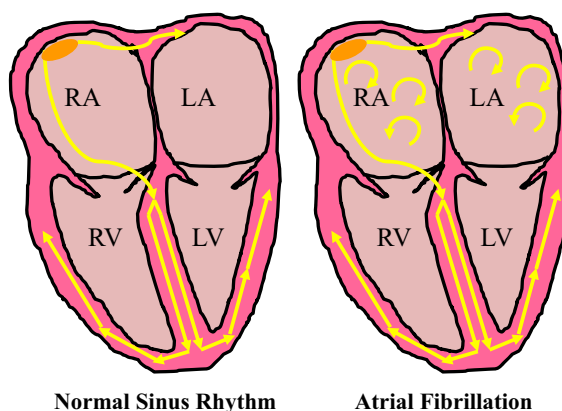


FIGURE 7.12 In normal sinus rhythm, an electrical impulse (yellow arrows) (left) is initiated in the sinoatrial (SA) node (orange). It moves across interatrial tracts that spread the signal across the left and right atria. The electrical impulse then passes through the atrioventricular (AV) node and into the ventricles, where it spreads across interventricular tracts. In atrial fibrillation (right), the interatrial tracts of the atrial chambers have become distorted, creating opportunities for aberrant electrical impulses (short circuits) that disrupt the normal sinus rhythm. The disruption presents clinically as an irregular and often rapid heartbeat in the atrial chambers of the heart. RA, right auricle; RV, right ventricle; LA, left auricle; LV, left ventricle.

of hundreds of regions of the atrial chamber of the heart (Figure 7.12), which decreases atrial blood transport and increases the rate of ventricular response. Globally, over 33 million people suffer from this condition, and the development of novel antiarrhythmic agents remains a challenge.³³