TABLE 273e-1 ARRHYTHMIA MECHANISMS

Electrophysiologic Property	Molecular Components	Mechanism	Prototypic Arrhythmias
Cellular			
Impulse Initiation			
Automaticity	I_f, $I_{Ca\text{-}L}$, $I_{Ca\text{-}T}$, I_K, I_{K1}	Suppression/ acceleration of phase 4	Sinus bradycardia, sinus tachycardia
Triggered automaticity	Calcium overload, I_{Ti}	DADs	Digitalis toxicity, reperfusion VT
	$I_{Ca\text{-}L}$, I_K, I_{Na}	EADs	Torsades des pointes, congenital and acquired
Excitation	I_{Na}	Suppression of phase 0	Ischemic VF
	$I_{K\text{-}ATP}$	AP shortening, inexcitability	
	$I_{Ca\text{-}L}$	Suppression	AV block
Repolarization	I_{Na}, $I_{Ca\text{-}L}$, I_K, I_{K1}, Ca^{2+} homeostasis	AP prolongation, EADs, DADs	Polymorphic VT (HF, LVH)
	$I_{Ca\text{-}L}$, K channels, Ca^{2+} homeostasis	AP shortening	Atrial fibrillation
Multicellular			
Cellular Coupling	Connexins (Cx43), I_{Na}, $I_{K\text{-}ATP}$	Decreased coupling	Ischemic VT/VF
Tissue Structure	Extracellular matrix, collagen	Excitable gap and functional reentry	Monomorphic VT, atrial fibrillation

Abbreviations: AP, action potential; AV, atrioventricular; DADs, delayed afterdepolarizations; EADs, early afterdepolarizations; HF, heart failure; LVH, left ventricular hypertrophy; VF, ventricular fibrillation; VT, ventricular tachyarrhythmia.

(AV) nodes, His-Purkinje system, coronary sinus, and pulmonary veins. Phase 4 depolarization results from the concerted action of a number of ionic currents, including K^+ currents, Ca^{2+} currents, electrogenic Na, K-ATPase, the Na-Ca exchanger, and the so-called funny, or pacemaker, current (I_f); however, the relative importance of these currents remains controversial.

The rate of phase 4 depolarization and, therefore, the firing rates of pacemaker cells are dynamically regulated. Prominent among the factors that modulate phase 4 is autonomic nervous system tone. The negative chronotropic effect of activation of the parasympathetic nervous system is a result of the release of acetylcholine that binds to muscarinic receptors, releasing G protein βγ subunits that activate a potassium current (I_{KACh}) in nodal and atrial cells. The resulting increase in K^+ conductance opposes membrane depolarization, slowing the rate of rise of phase 4 of the action potential. Conversely, augmentation of sympathetic nervous system tone increases myocardial catecholamine concentrations, which activate both α- and β-adrenergic receptors. The effect of β_1-adrenergic stimulation predominates in pacemaking cells, augmenting both L-type Ca current ($I_{Ca\text{-}L}$) and I_f, thus increasing the slope of phase 4. Enhanced sympathetic nervous system activity can dramatically increase the rate of firing of SA nodal cells, producing sinus tachycardia with rates >200 beats/min. By contrast, the increased rate of firing of Purkinje cells is more limited, rarely producing ventricular tachyarrhythmias >120 beats/min.

Normal automaticity may be affected by a number of other factors associated with heart disease. Hypokalemia and ischemia may reduce the activity of Na, K-ATPase, thereby reducing the background repolarizing current and enhancing phase 4 diastolic depolarization. The end result would be an increase in the spontaneous firing rate of pacemaking cells. Modest increases in extracellular potassium may render the maximum diastolic potential more positive, thereby also increasing the firing rate of pacemaking cells. A more significant increase in $[K^+]_o$, however, renders the heart inexcitable by depolarizing the membrane potential.

Normal or enhanced automaticity of subsidiary latent pacemakers produces escape rhythms in the setting of failure of more dominant pacemakers. Suppression of a pacemaker cell by a faster rhythm leads to an increased intracellular Na^+ load ($[Na^+]_i$), and extrusion of Na^+ from the cell by Na, K-ATPase produces an increased background repolarizing current that slows phase 4 diastolic depolarization. At slower rates, $[Na^+]_i$ is decreased, as is the activity of the Na, K-ATPase, resulting in progressively more rapid diastolic depolarization and warm-up of the tachycardia rate. Overdrive suppression and warm-up are characteristic of, but may not be observed in, all automatic tachycardias. Abnormal conduction into tissue with enhanced automaticity (*entrance block*) may blunt or eliminate the phenomena of overdrive suppression and warm-up of automatic tissue.

Abnormal automaticity may produce atrial tachycardia, accelerated idioventricular rhythms, and ventricular tachycardia, particularly associated with ischemia and reperfusion. It has also been suggested that injury currents at the borders of ischemic myocardium may depolarize adjacent nonischemic tissue, predisposing to automatic ventricular tachycardia.

Afterdepolarizations and Triggered Automaticity Triggered automaticity or activity refers to impulse initiation that is dependent on afterdepolarizations (Fig. 273e-3). Afterdepolarizations are membrane voltage oscillations that occur during (early afterdepolarizations, EADs) or after (delayed afterdepolarizations, DADs) an action potential.

The cellular feature common to the induction of DADs is the presence of an increased Ca^{2+} load in the cytosol and sarcoplasmic reticulum. Digitalis glycoside toxicity, catecholamines, and ischemia all can enhance Ca^{2+} loading sufficiently to produce DADs. Accumulation of lysophospholipids in ischemic myocardium with consequent Na^+ and Ca^{2+} overload has been suggested as a mechanism for DADs and triggered automaticity. Cells from damaged areas or cells that survive a myocardial infarction may display spontaneous release of calcium from the sarcoplasmic reticulum, and this may generate "waves" of intracellular calcium elevation and arrhythmias.

EADs occur during the action potential and interrupt the orderly repolarization of the myocyte. Traditionally, EADs have been thought to arise from action potential prolongation and reactivation of depolarizing currents, but more recent experimental evidence suggests a previously unappreciated interrelationship between intracellular calcium loading and EADs. Cytosolic calcium may increase when action potentials are prolonged. This, in turn, appears to enhance L-type Ca current, further prolonging action potential duration as well as providing the inward current driving EADs. Intracellular calcium loading by action potential prolongation may also enhance the likelihood of DADs. The interrelationship among intracellular $[Ca^{2+}]$, EADs, and DADs may be one explanation for the susceptibility of hearts that are

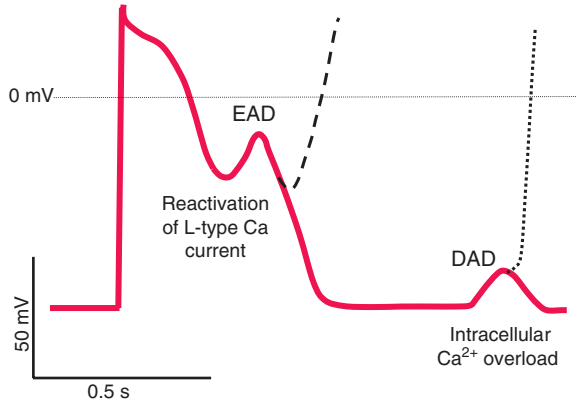

FIGURE 273e-3 Schematic action potentials with early afterdepolarizations (EADs) and delayed afterdepolarizations (DADs). Afterdepolarizations are spontaneous depolarizations in cardiac myocytes. EADs occur before the end of the action potential (phases 2 and 3), interrupting repolarization. DADs occur during phase 4 of the action potential after completion of repolarization. The cellular mechanisms of EADs and DADs differ (see text).