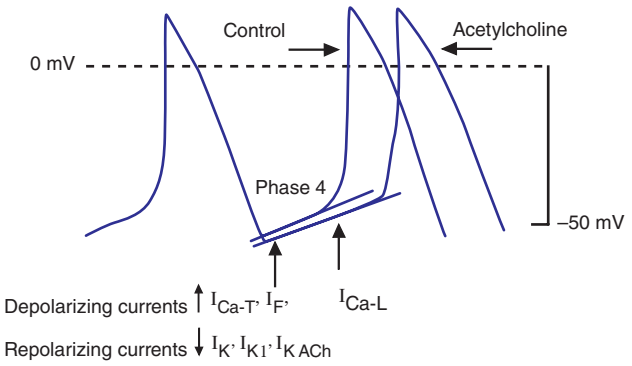

FIGURE 274-2 Schematics of nodal action potentials and the currents that contribute to phase 4 depolarization. Relative increases in depolarizing L- (I_{Ca-L}) and T- (I_{Ca-T}) type calcium and pacemaker currents (I_f) along with a reduction in repolarizing inward rectifier (I_{K1}) and delayed rectifier (I_K) potassium currents result in depolarization. Activation of ACh-gated (I_{KACh}) potassium current and beta blockade slow the rate of phase 4 and decrease the pacing rate. *(Modified from J Jalife et al: Basic Cardiac Electrophysiology for the Clinician, Blackwell Publishing, 1999.)*

Irregular and slow propagation of impulses from the SA node can be explained by the electrophysiology of nodal cells and the structure of the SA node itself. The action potentials of SA nodal cells are characterized by a relatively depolarized membrane potential (Fig. 274-1) of −40 to −60 mV, slow phase 0 upstroke, and relatively rapid phase 4 diastolic depolarization compared with the action potentials recorded in cardiac muscle cells. The relative absence of inward rectifier potassium current (I_{K1}) accounts for the depolarized membrane potential; the slow upstroke of phase 0 results from the absence of available fast sodium current (I_{Na}) and is mediated by L-type calcium current (I_{Ca-L}); and phase 4 depolarization is a result of the aggregate activity of a number of ionic currents. Prominently, both L- and T-type (I_{Ca-T}) calcium currents, the pacemaker current (so-called funny current, or I_f) formed by hyperpolarization-activated cyclic nucleotide-gated channels, and the electrogenic sodium-calcium exchanger provide depolarizing current that is antagonized by delayed rectifier (I_{Kr}) and acetylcholine-gated (I_{KACh}) potassium currents. I_{Ca-L}, I_{Ca-T}, and I_f are modulated by β-adrenergic stimulation and I_{KACh} by vagal stimulation, explaining the exquisite sensitivity of diastolic depolarization to autonomic nervous system activity. The slow conduction within the SA node is explained by the absence of I_{Na} and poor electrical coupling of cells in the node, resulting from sizable amounts of interstitial tissue and a low abundance of gap junctions. The poor coupling allows for graded electrophysiologic properties within the node, with the peripheral transitional cells being silenced by electrotonic coupling to atrial myocardium.

TABLE 274-1 ETIOLOGIES OF SA NODE DYSFUNCTION

Extrinsic	Intrinsic
Autonomic	Sick-sinus syndrome (SSS)
Carotid sinus hypersensitivity	Coronary artery disease (chronic and acute MI)
Vasovagal (cardioinhibitory) stimulation	Inflammatory
Drugs	Pericarditis
Beta blockers	Myocarditis (including viral)
Calcium channel blockers	Rheumatic heart disease
Digoxin	Collagen vascular diseases
Ivabradine	Lyme disease
Antiarrhythmics (class I and III)	Senile amyloidosis
Adenosine	Congenital heart disease
Clonidine (other sympatholytics)	TGA/Mustard and Fontan repairs
Lithium carbonate	Iatrogenic
Cimetidine	Radiation therapy
Amitriptyline	Postsurgical
Phenothiazines	Chest trauma
Narcotics (methadone)	Familial
Pentamidine	SSS2, AD, OMIM #163800 (15q24-25)
Hypothyroidism	SSS1, AR OMIM #608567 (3p21)
Sleep apnea	SSS3, AD, OMIM #614090 (14q11.2)
Hypoxia	SA node disease with myopia, OMIM #182190
Endotracheal suctioning (vagal maneuvers)	Kearns-Sayre syndrome, OMIM #530000
Hypothermia	Myotonic dystrophy
Increased intracranial pressure	Type 1, OMIM #160900 (19q13.2-13.3)
	Type 2, OMIM #602668 (3q13.3-q24)
	Friedreich's ataxia, OMIM #229300 (9q13, 9p23-p11)

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; MI, myocardial infarction; OMIM, Online Mendelian Inheritance in Man (database); TGA, transposition of the great arteries.

ETIOLOGY OF SA NODAL DISEASE

SA nodal dysfunction has been classified as intrinsic or extrinsic. The distinction is important because extrinsic dysfunction is often reversible and generally should be corrected before pacemaker therapy is considered (Table 274-1). The most common causes of extrinsic SA node dysfunction are drugs and autonomic nervous system influences that suppress automaticity and/or compromise conduction. Other extrinsic causes include hypothyroidism, sleep apnea, and conditions likely to occur in critically ill patients such as hypothermia, hypoxia, increased intracranial pressure (Cushing's response), and endotracheal suctioning via activation of the vagus nerve.

Intrinsic sinus node dysfunction is degenerative and often is characterized pathologically by fibrous replacement of the SA node or its connections to the atrium. Acute and chronic coronary artery disease (CAD) may be associated with SA node dysfunction, although in the setting of acute myocardial infarction (MI; typically inferior), the abnormalities are transient. Inflammatory processes may alter SA node function, ultimately producing replacement fibrosis. Pericarditis, myocarditis, and rheumatic heart disease have been associated with SA nodal disease with sinus bradycardia, sinus arrest, and exit block. Carditis associated with systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and mixed connective tissue disorders (MCTDs) may also affect SA node structure and function. Senile amyloidosis is an infiltrative disorder in patients typically in the ninth decade of life; deposition of amyloid protein in the atrial myocardium can impair SA node function. Some SA node disease is iatrogenic and results from direct injury to the SA node during cardiothoracic surgery.

Rare heritable forms of sinus node disease have been described, and several have been characterized genetically. Autosomal dominant sinus node dysfunction in conjunction with supraventricular tachycardia (i.e., tachycardia-bradycardia variant of sick-sinus syndrome [SSS2]) has been linked to mutations in the pacemaker current (I_f) subunit gene *HCN4* on chromosome 15. An autosomal recessive form of SSS1 with the prominent feature of atrial inexcitability and absence of P waves on the electrocardiogram (ECG) is caused by mutations in the cardiac sodium channel gene, *SCN5A*, on chromosome 3. Variants in myosin heavy chain 6 (*MYH6*) increase the susceptibility to SSS (SSS3). SA node dysfunction associated with myopia has been described but not genetically characterized. There are several neuromuscular diseases, including Kearns-Sayre syndrome (ophthalmoplegia, pigmentary degeneration of the retina, and cardiomyopathy) and myotonic dystrophy, that have a predilection for the conducting system and SA node.

SSS in both the young and the elderly is associated with an increase in fibrous tissue in the SA node. The onset of SSS may be hastened by coexisting disease, such as CAD, diabetes mellitus, hypertension, and valvular diseases and cardiomyopathies.

CLINICAL FEATURES OF SA NODE DISEASE

SA node dysfunction may be completely asymptomatic and manifest as an ECG anomaly such as sinus bradycardia; sinus arrest and