Sick Sinus Syndrome

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KEYWORDS

• Sinus node • Bradycardia • Sick sinus syndrome • Bradycardia-tachycardia syndrome
• Sinus node dysfunction • Sinus arrest • Sinoatrial block

KEY POINTS

- The sick sinus syndrome includes a spectrum of symptoms and heart rhythm disturbances related to abnormal sinus impulse formation and/or propagation.
- This disease has different electrocardiographic presentations, such as bradycardia, sinus arrest, sinoatrial block, and alternant episodes of bradycardia and tachycardia.
- Symptoms related to these heart rhythm disturbances are generally fatigue, effort dyspnea, dizziness, syncope or presyncope, and palpitations, although patients can be asymptomatic in the early phase of the disease.
- When symptoms are related to intrinsic dysfunction of the sinus node, pacemaker implantation is required, whereas when a reversible cause is present, identification and correction of this extrinsic cause are necessary.
- Diagnosis is mainly based on clinical and electrocardiographic evaluation, but in some cases, further noninvasive and invasive diagnostic workup may be required.

INTRODUCTION

The sinus node (SN) is located in the superior right atrium and is the natural pacemaker of the human heart.[1] The electrical activity of the SN is under a precise regulation of the autonomous nervous system that allows it to adjust the heart rate according to the body's needs.[2] The sick sinus syndrome includes symptoms and signs related to abnormal sinus impulse formation and/or propagation caused by intrinsic sinus node dysfunction (SND). This heterogeneous clinical entity includes rhythm disturbances, which may lead to major cardiovascular events,[3] thromboembolism,[4] inadequate heart rate response to exercise/stress known as chronotropic incompetence, or any other symptom requiring pacemaker implantation. The annual number of new cases with sick sinus syndrome in the United States is expected to increase from 78,000 in 2012 to 172,000 in 2060.[5]

ETIOLOGY AND PATHOPHYSIOLOGY

The different forms of primary and secondary SND are listed in **Table 1**. SND is better conceptualized as a spectrum of disorders, rather than a single entity, where different pathophysiologic mechanisms lead to a very similar disease phenotype.

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Table 1
Different forms of primary and secondary sinus node dysfunction

Primary SND	SND Secondary to Reversible Causes
Degenerative fibrosis • Aging • Atrial tachyarrhythmias • Chronic ischemia (?) Genetic • Inherited primary arrhythmia syndromes with mutations for SCN5A, HCN4, calsequestrin, ryanodine Associated with atrial myopathy: • Amyloidosis • Connective tissue diseases • Hemochromatosis • Sarcoidosis • Hereditary muscle dystrophies • Myocarditis • Valvular heart disease • Heart failure • Hypertension • Diabetes • Obesity • Obstructive sleep apnea Infective • Rheumatic fever • Chagas disease • Diphtheria	Metabolic disorders • Hyperkalemia • Hypocalcemia • Hypothermia • Hypoxia • Acute ischemia Pharmacologic agents • Antiarrhythmic medication (class I and III) • β-Blockers • Calcium channel blockers (nondihydropyridine) • Digoxin • Cimetidine • Clonidine, methyldopa, reserpine • Lithium, phenothiazine, amitriptyline Extracardiac diseases • Hypothyroidism • Intracranial hypertension

Degenerative Fibrosis

Aging causes both a decrease in the intrinsic heart rate and an increase in SN conduction time.[6] The latter could be well explained by atrial remodeling, more evident in the region around the crista terminalis, leading to conduction slowing and voltage loss and evidence of a decrease in SN reserve.[7] Indeed, previous experimental[8] and clinical studies[7] showed that aging was associated with a significant increase in the atrial effective refractory period and prolonged conduction time associated with areas of low voltage and double potentials consistent with age-related development of interstitial fibrosis. Furthermore, in patients with normal heart and no previous history of atrial fibrillation (AF), electroanatomic mapping of the right and left atrium[9] showed an inverse correlation between age and left atrial wavelength, which may explain the age-related modifications of the atrial substrate and the increase in the prevalence of AF. Hence, the association between SND and atrial tachyarrhythmias observed during aging favors the hypothesis that these 2 entities share several pathophysiologic aspects and interstitial atrial fibrosis is a possible link. Earlier in 1954, aging was first noted to be associated with fibrosis of the SN.[10] However, fibrosis cannot explain all cases of SND. Although morphologic studies in the 1970s[11,12] revealed that most cases of patients with SND were associated with SN fibrosis, the same studies showed that other patients with the same clinical presentation had normal SN histology. In experimental studies, widespread electrical remodeling with loss of connexin 43,[13] age-related changes in the expression of ion channels and clock genes in the SN,[14] and downregulation of genes responsible for collagen and elastin[15] have been advocated as possible causes of SND. Therefore, aging is associated with both structural and molecular remodeling, and the cause of SND in the elderly is likely to be complex and heterogeneous.

As mentioned earlier, atrial structural alterations leading to SND predispose also to the development of atrial arrhythmias. However, AF per se could also cause SND. In dogs, pacing-induced chronic AF causes SND and a reversible electrical remodeling with atrial conduction time prolongation and shortening of atrial refractoriness, which favors perpetuation of AF.[16] In patients undergoing electrical cardioversion of long-standing persistent AF, a depressed SN function is observed, which is independent from the autonomic tone and recovers after sinus rhythm restoration, suggesting that AF remodels the SN.[17] More recently, in a canine model,[18] it has been demonstrated that atrial tachyarrhythmias downregulate ion channel expression in the SN, particularly the pacemaker subunit I(f), which may contribute to worsening SND when AF is concomitantly present. These data highlight the pathophysiologic bi-univocal relationship between SND and atrial arrhythmias.

Although acute myocardial ischemia is listed (see **Table 1**) among the causes of reversible SND,[19] whether chronic ischemia is a cause of SND is controversial. In fact, data from morphologic studies that in the past investigated the role of chronic ischemia of SN function showed mixed results,[20] and a definite conclusion cannot be reached.