# Sick Sinus Syndrome

# 22

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**Key Points**

- Syncope in the context of SSS is frequently abrupt and lacks typical prodromal symptoms.
- Syncope is frequently precipitated by sinus pauses following sinus node overdrive by atrial tachyarrhythmias such as atrial fibrillation.
- The diagnosis of SSS is usually obtained by combining clinical presentation and typical ECG findings that disclose evidence of sinus node dysfunction.
- Treatment is usually achieved by implanting a permanent pacemaker with complete resolution of syncope.

## 22.1 Introduction

The sinoatrail node (SAN), the dominant pacemaker in the heart, was originally described by Keith and Flack in 1907 [1]. The SAN is a subepicardial structure located at the junction of the right atrium and the superior vena cava [1]. The SAN spontaneous firing activity is not completely understood. Two predominant

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mechanisms are proposed to serve as the initiation of the sinus activity: The If channels (sodium and potassium ionic currents) and spontaneous intracellular calcium released by sarcoplasmic reticulum [2]. These two mechanisms are not mutually exclusive, and current evidence suggests that they may be complementary in their pacemaker actions. The SAN is richly innervated by the autonomic nervous system and the balance between the parasympathetic and sympathetic inputs modulate pacemaker rate. The vagal parasympathetic nerves slow the SAN rate and are dominant at rest, while increased sympathetic nerve traffic as well as adrenal medullary release of catecholamines increase sinus rate during exercise and stress.

Sick Sinus Syndrome (SSS) is characterized by dysfunction of the SAN secondary to gradual deterioration of the pacemaker cells and the surrounding atrial myocardium. The term was first coined by Ferrer et al. in 1968 [3] and is now commonly used to describe the inability of the SAN to generate a heart rate that meets the physiological needs of an individual [4]. Moreover, SAN remodeling in atrial tachyarrhythmias can be triggered by persistent changes in atrial physiology that result in increased vulnerability to further arrhythmias, particularly atrial fibrillation [4]. These abnormalities can lead to profound sinus bradycardia, sinus pauses, cardiac sinus arrest, and sinoatrial exit blocks. SSS is frequently associated with paroxysmal atrial fibrillation and manifests clinically as the bradycardia–tachycardia syndrome.

The clinical presentation, etiology, natural history, diagnosis and evaluation, as well as treatment of SSS will be reviewed in this chapter.

## 22.2 Clinical Characteristics

The clinical manifestations of SND are diverse, reflecting the range of typical sinoatrial rhythm disturbances. The most dramatic presentation is syncope and is associated with an abrupt pause in sinus impulse formation or sinus exit block, either spontaneously or after the termination of an atrial tachyarrhythmia, that causes cerebral hypoperfusion. The pause in sinus node activity is frequently accompanied by an inadequate, delayed, or absent response of subsidiary escape pacemakers in the AV junction or ventricular myocardium, which aggravates the hemodynamic consequences. The initial diagnosis of SSS is often clinical and patients may present with symptoms of dizziness, lightheadedness, syncope, shortness of breath on exertion, angina, and/or palpitations. Patients with symptomatic SSS are frequently older, have multiple comorbidities and high mortality rate. Clinical trials comparing pacing modes in patients with sinus node dysfunction have shown a mean age of 73–76 years and both genders are equally affected [5, 6].

SSS is defined by electrocardiographic criteria since clinical signs and symptoms may vary significantly. It is important to highlight that sinus bradycardia does not always confirm the presence of SSS (i.e., increase vagal tone (athletes) and medications that slow sinus rate). The characteristics of SSS include:

- Frequent events of inappropriate and often severe bradycardia [3].
- Sinus pauses, arrest and sinoatrial exit block with and, often, without appropriate atrial or junctional escape rhythms. The failure of timely rate response leading to extreme bradycardia and asystole can lead to syncope [3].
- Alternating bradycardia and atrial tachyarrhythmias [7]. Most commonly, atrial fibrillation (AF) but atrial flutter and paroxysmal supraventricular tachycardias can also occur. These can be triggered by a prolonged sinus node recovery time after spontaneous conversion from the tachyarrhythmia.
- The electrocardiographic manifestation may occur with or without symptoms.

## 22.3 Etiology

SSS occurs as a result of disorders in automaticity, conduction, or both. Abnormal automaticity, or sinus arrest refers to a failure of sinus impulse generation while abnormal conduction, or sinoatrail delay or block, is a failure of impulse transmission. These disorders may be the result of several different mechanisms. The most common cause of SSS is the replacement of the sinus node tissue by fibrotic tissue, which may be accompanied by degeneration and fibrosis of the conduction system including AV node [8]. Moreover, atherosclerosis, inflammatory processes, or embolic diseases can compromise the blood supply through the SAN artery [9]. Finally, SSS is less often due to a variety of disorders:

- Infiltrative diseases such as amyloidosis, sarcoidosis, scleroderma, hemochromatosis, and sometimes tumors [9]
- Epicardial and pericardial disease [9]
- Infectious diseases with inflammatory features (Chagas's disease, Lyme disease, etc.)
- Drugs such as parasympathicomimetic agents, sympatholytics, digoxin, calcium channel blockers, and lithium
- Toxins such as grayanotoxin produced by some plants and found in certain variety of honey [10]
- Cardiac trauma during surgery may affect the SAN directly or its blood supply
- Congenital and acquire heart disease as well as rare familial cases of SSS associated with specific gene mutations [11]

## 22.4 Natural History

SSS evolves with time. There are variable, and often long, periods of normal sinus node function [12]. Nevertheless, once present, SSS eventually progresses and manifests in most patients. Lien et al. [12] reported that, in patients presenting with sinus bradycardia associated with SAN block and SAN arrest, an average of 13 years were needed for progression to complete SAN dysfunction. Overall intrinsic sinus node function tends to deteriorate with age [13]. Atrial arrhythmias and conduction

disturbances become more common over time increasing the likelihood of SSS. Overall, patients with SSS are at increased risk of cardiovascular events including syncope, heart failure, chronic AF, or poorly tolerated atrial arrhythmias [13]. Multivariate analysis of cohort studies has identified independent predictors of a cardiovascular event including age, left ventricular end-diastolic diameter, and left ventricular ejection fraction. Independent predictors of syncope were a history of syncope and corrected sinus node recovery time ≥800 ms.

Finally, the mortality of patients with SSS is significant and not always due to cardiac causes. In the MOST trial [14], 2,010 patients (median age 74 years) were studied; 404 (20 %) died at a median of 33 months of follow-up. The cause of death was cardiac in 35 %, noncardiac in 49 %, and unknown in 16 %. Independent predictors of death included age, male sex, weight, prior myocardial infarction, cardiomyopathy, and measures of functional status and other comorbidities.

## 22.5 Diagnosis and Evaluation

The diagnosis and evaluation of SSS include both physiologic and pharmacologic testing. A number of different modalities have been used in the evaluation of suspected SSS:

- ECG: The diagnosis of SSS in persons with suggestive symptoms is often made from the surface ECG. The typical ECG manifestations were discussed in the clinical characteristics section of this chapter.
- Ambulatory ECG monitoring (Holter) and event recording have the potential advantage of prolonged ECG monitoring for days and weeks, and allows the correlation of symptoms with cardiac arrhythmias [15]. In patients suspected of having SSS, ambulatory ECG monitoring may provide important clues in 50–70 % of cases [15, 16]. In some cases, when the symptoms are infrequent, implantable loop recorders have been used for monitoring periods greater than 1 year [17].
- Exercise testing: Inappropriate increase in heart rate after exercise may be useful in the diagnosis of SSS (chronotropic incompetence) [18]. Clinicians diagnose chronotropic incompetence as either a near-constant nontachycardic heart rate over a 24 h period or the inability of achieving at least 80 % of the maximum predicted heart rate with exercise testing according to age and gender [18].
- Intrinsic heart rate (IHR) is defined as the heart rate after complete pharmacological autonomic blockade of the sinus node. This is achieved with the simultaneous intravenous administration of propranolol (0.2 mg/kg) and atropine (0.04 mg/kg) [19]. The IHR helps discriminate patients with intrinsic SSS (reflecting primary SA node dysfunction) from those who have bradycardia from extrinsic causes such as increased parasympathetic tone or drugs [20]. Intrinsic SSS is presumed to be present if the sinus rate does not exceed the predicted IHR after atropine. A normal IHR suggests extrinsic causes.
- Invasive electrophysiological studies (EPS) are not commonly used for the evaluation of SSS because of their limited sensitivity in eliciting

bradyarrhythmic abnormalities [15]. The salient aspects of electrophysiology studies that aid in eliciting a bradyarrhythmic abnormality include assessment of the sinoatrial node recovery time (SNRT), sinoatrial conduction time and corrected SNRT, and the sinus node and atrial tissue refractory periods [21]. cSNRT is perhaps the most useful test of overall sinus node automaticity. The concept is simple. The atria are driven rapidly; a normal SA node will have a recovery time within certain limits, while recovery will be delayed in a depressed or sick sinus node [22].

## 22.6 Treatment

The only treatment option available for symptomatic SSS is permanent pacing. Mode and selection of type of pacing are out of the scope of this review and current guideline recommendations are summarized in Table 22.1 [23]. The goal of pacing is to reduce the recurrence of syncope and presyncope and to improve chronotropic incompetence.

**Table 22.1** Recommendations for permanent pacing in sinus node dysfunction [23]

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| Class I |
| 1. Permanent pacemaker implantation is indicated for SND with documented symptomatic bradycardia, including frequent sinus pauses that produce symptoms. (Level of Evidence: C) |
| 2. Permanent pacemaker implantation is indicated for symptomatic chronotropic incompetence. (Level of Evidence: C) |
| 3. Permanent pacemaker implantation is indicated for symptomatic sinus bradycardia that results from required drug therapy for medical conditions. (Level of Evidence: C) |
| Class IIa |
| 1. Permanent pacemaker implantation is reasonable for SND with heart rate less than 40 bpm when a clear association between significant symptoms consistent with bradycardia and the actual presence of bradycardia has not been documented. (Level of Evidence: C) |
| 2. Permanent pacemaker implantation is reasonable for syncope of unexplained origin when clinically significant abnormalities of sinus node function are discovered or provoked in electrophysiological studies. (Level of Evidence: C) |
| Class IIb |
| 1. Permanent pacemaker implantation may be considered in minimally symptomatic patients with chronic heart rate less than 40 bpm while awake. (Level of Evidence: C) |
| Class III |
| 1. Permanent pacemaker implantation is not indicated for SND in asymptomatic patients. (Level of Evidence: C) |
| 2. Permanent pacemaker implantation is not indicated for SND in patients for whom the symptoms suggestive of bradycardia have been clearly documented to occur in the absence of bradycardia. (Level of Evidence: C) |
| 3. Permanent pacemaker implantation is not indicated for SND with symptomatic bradycardia due to nonessential drug therapy. (Level of Evidence: C) |

## References


1. Keith A, Flack M (1907) The form and nature of the muscular connections between the primary divisions of the vertebrate heart. J Anat Physiol 41:172
2. Lakatta EG, Maltsev VA, Vinogradova TM (2010) A coupled SYSTEM of intracellular Ca2+ clocks and surface membrane voltage clocks controls the timekeeping mechanism of the heart's pacemaker. Circ Res 106:659
3. Ferrer MI (1968) The sick sinus syndrome in atrial disease. JAMA 206:645
4. Dobrzynski H, Boyett MR, Anderson RH (2007) New insights into pacemaker activity: promoting understanding of sick sinus syndrome. Circulation 115:1921
5. Lamas GA, Lee KL, Sweeney MO et al (2002) Ventricular pacing or dual-chamber pacing for sinus-node dysfunction. N Engl J Med 346:1854
6. Connolly SJ, Kerr CR, Gent M et al (2000) Effects of physiologic pacing versus ventricular pacing on the risk of stroke and death due to cardiovascular causes. Canadian Trial of Physiologic Pacing Investigators. N Engl J Med 342:1385
7. Gomes JA, Kang PS, Matheson M et al (1981) Coexistence of sick sinus rhythm and atrial flutter-fibrillation. Circulation 63:80
8. Thery C, Gosselin B, Lekieffre J, Warembourg H (1977) Pathology of sinoatrial node. Correlations with electrocardiographic findings in 111 patients. Am Heart J 93:735
9. James TN (1977) The sinus node. Am J Cardiol 40:965
10. Lennerz C, Jilek C, Semmler V et al (2012) Sinus arrest from mad honey disease. Ann Intern Med 157:755
11. Caralis DG, Varghese PJ (1976) Familial sinoatrial node dysfunction. Increased vagal tone a possible aetiology. Br Heart J 38:951
12. Lien WP, Lee YS, Chang FZ et al (1977) The sick sinus syndrome: natural history of dysfunction of the sinoatrial node. Chest 72:628
13. Kuga K, Yamaguchi I, Sugishita Y, Ito I (1988) Assessment by autonomic blockade of age-related changes of the sinus node function and autonomic regulation in sick sinus syndrome. Am J Cardiol 61:361
14. Glotzer TV, Hellkamp AS, Zimmerman J et al (2003) Atrial high rate episodes detected by pacemaker diagnostics predict death and stroke: report of the Atrial Diagnostics Ancillary Study of the MOde Selection Trial (MOST). Circulation 107:1614
15. Reiffel JA, Bigger JT Jr, Cramer M, Reid DS (1977) Ability of Holter electrocardiographic recording and atrial stimulation to detect sinus nodal dysfunction in symptomatic and asymptomatic patients with sinus bradycardia. Am J Cardiol 40:189
16. Lipski J, Cohen L, Espinoza J et al (1976) Value of Holter monitoring in assessing cardiac arrhythmias in symptomatic patients. Am J Cardiol 37:102
17. Kinlay S, Leitch JW, Neil A et al (1996) Cardiac event recorders yield more diagnoses and are more cost-effective than 48-hour Holter monitoring in patients with palpitations. A controlled clinical trial. Ann Intern Med 124:16
18. Zimetbaum PJ, Josephson ME (1999) The evolving role of ambulatory arrhythmia monitoring in general clinical practice. Ann Intern Med 130:848
19. Jose AD, Collison D (1970) The normal range and determinants of the intrinsic heart rate in man. Cardiovasc Res 4:160
20. Opthof T (2000) The normal range and determinants of the intrinsic heart rate in man. Cardiovasc Res 45:177
21. Narula OS, Samet P, Javier RP (1972) Significance of the sinus-node recovery time. Circulation 45:140
22. Gupta PK, Lichstein E, Chadda KD, Badui E (1974) Appraisal of sinus nodal recovery time in patients with sick sinus syndrome. Am J Cardiol 34:265
23. Epstein AE, DiMarco JP, Ellenbogen KA (2013) 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 61(3):e6–e75. doi:10.1016/j.jacc.2012.11.007