

SINUS BRADYCARDIA AND SINUS NODAL DISEASE

SINUS BRADYCARDIA

Definitions

Sinus rates <60 beats/min are defined as bradycardia in adults. ¹ Lower rates are common in well-trained athletes, and, occasionally, in the young. During sleep the sinus rate may fall to 35 beats/min with pauses up to 3 sec and is not considered abnormal. Resting bradycardia (HR $\leq$ 40 bpm) and pauses of 2 to 3 s are present in a significant proportion of endurance athletes.²

Sinus arrhythmia usually refers to sinus cycle phasic variation that is related to the respiratory cycle and is normal in the youth. Non-respiratory sinus arrhythmia may be seen with digitalis toxicity.

Sinus arrest (sinus pauses) manifests itself as pauses with the P-P interval containing the pause not being equal or multiple of the basic P-P interval.

In **sinoatrial exit block** (first, second or third degree) the atrium is not depolarized despite the sinus stimulus and the duration of the pause is a multiple of the basic P-P interval.

Wandering pacemaker refers to shift of the dominant pacemaker from the sinus node to other atrial focus, usually lower at the crista terminalis. It is a normal finding, especially in athletes. Asymptomatic bradycardia does not require treatment, and no drugs increase efficiently and safely the heart rate. Pacing is considered only in the presence of bradycardia-induced low cardiac output state.

Aetiology

Intracranial and mediastinal tumors, severe hypoxia, hypothermia, myxedema, mental depression and antiarrhythmic drugs such as beta blockers (orally or by conjunctival instillation for glaucoma), amiodarone, and others may cause sinus bradycardia. Transient sinus bradycardia occurs in 10-25% patients with acute MI (usually inferior) but is an ominous sign if it occurs following resuscitation from cardiac arrest. ³ Intense training has also been associated with bradyarrhythmias, including both sick sinus syndrome and AV block.⁴ Exercise-induced bradycardia is not always reversible and may necessitate future pacemaker implantation. In a Swedish Register, male endurance skiers had a higher incidence of bradycardia and pacemaker implantation, but this did not result in higher mortality rates.⁵ Although sinus node dysfunction and atrial arrhythmias frequently coexist, the putative mechanism remains unclear.⁶ Medications and conditions associated with bradycardia are presented in the Chapter on Disorders of CCS. A causal role for AF in the

development of SSS has been demonstrated.⁷ Genetic causes of sinus bradycardia and SSS are presented in Table 1.

SINUS NODAL DISEASE

Definition

Sinus nodal disease (SND) or sick sinus syndrome (SSS) refers to any of the following conditions that may co-exist (Table 2):

1. Persistent spontaneous bradycardia <50 bpm not caused by drugs with or without chronotropic incompetence, ie inability to achieve 85% of the age-predicted maximum heart rate on the treadmill.^{1, 8}
2. Sinus pauses >3s either due to sinus arrest or exit block.
3. Alternating episodes of bradycardia usually following tachycardia (mostly AF).

Sinus nodal disease is one of the most common cause of bradyarrhythmias requiring pacing in the western world.

Epidemiology

In the United States, the number of new cases of sick sinus syndrome per year are expected to rise from 78 000 in 2012 to 172 000 in 2060.⁹ SND is primarily a disease of the elderly, with an average of 68 years of age, equally affecting both sexes but being more prevalent in whites than in blacks.¹⁰

Pathophysiology

Age-dependent progressive fibrotic or degenerative destruction of the sinus node, its atrial radiations, and the surrounding nerves, and, perhaps, sinus nodal occlusion comprise the pathological basis of the disease.¹¹ Genetic causes of SSS are due to mutations in genes that encode for ion channels, such as the hyperpolarization-activated cyclic nucleotide channel 4 (HNC4), a major constituent of the pacemaker current (I_f) in the sinoatrial node, and genes KCNJ3 and KCNJ5. They may result in isolated sick sinus or other syndromes.¹²⁻¹⁴ Specific causes of sinus nodal disease are presented in Table 3. Bradycardia has been associated with lower cardiovascular disease risk in selected populations. However, in the MESA study, heart rate <50 bpm among middle-aged or older adults was generally not associated with incident cardiovascular disease or mortality except for a potential adverse association among those taking heart rate modifying drugs.¹⁵

Diagnosis

SND is primarily a disease of the elderly. Obesity, diabetes, RBBB, and elevated NT-proBNP are associated comorbidities.¹⁰ SSS is suspected when symptoms such as lightheadedness, fatigue, dizziness, and presyncope or syncope are related to bradycardia. Sinus nodal recovery time (SNRT) is derived at electrophysiology studies by pacing at the right atrium between 600 to 350 msec for 30-60 sec. This is corrected for the underlying sinus cycle length (cSNRT=SNRT-SCL). Values >525 msec are considered abnormal but only very prolonged cSNRT values (>800 ms) have reasonable predictive ability. This test, however, has limited sensitivity for the detection of SSS.¹⁶ The sino-atrial conduction time (SACT) is a very insensitive indicator being prolonged in only 40% of patients with clinical findings of SSS.¹⁶ Abnormal head-up tilt testing or carotid sinus massage in the presence of normal CSNRT suggest a vasodepressor reflex rather than SND (see Chapter on Syncope).¹⁷ Implantable monitoring devices may be useful in the presence of inconsistent symptoms.¹⁸

Initial evaluation of patients with suspected sinus node dysfunction is presented in Figure 1.

Therapy

Acute therapy

No drugs can effectively and safely increase the sinus rate. Acute therapy is presented in Figure 2, Table 4, and Figure 3 as well as in the Chapter on Disorders of CCS.

Chronic therapy

Indications for pacing are presented in Table 5 and 6 and Figure 4. In sinus node dysfunction, there is no established minimum heart rate or pause duration where permanent pacing is recommended.¹ Nocturnal bradycardia is not in itself an indication for permanent pacing. Establishing temporal correlation between symptoms and bradycardia is important when determining whether permanent pacing is needed. Minimally symptomatic patients may be just followed-up, unless if atrial tachycardias necessitate the use of beta blockers. The natural history of SND is variable, but the majority of patients who have experienced syncope due to sinus pause or bradycardia will have recurrent syncope. The incidence of sudden death, however, is extremely low, and SSS, treated or untreated does not affect survival.

Supraventricular tachycardia including AF occurs in approximately 30% of patients with sinus node dysfunction.^{19, 20} Subclinical atrial arrhythmias in patients who had a history of hypertension but no prior diagnosis of clinical atrial fibrillation, predispose to embolic events and these patients should be considered anticoagulation (see also Chapter 53).¹⁹ The risk of developing AV block within the next 5 years is 3-35%.¹

The *KCNJ3* gene encodes the inwardly rectifying potassium channel Kir3.1, which combines with Kir3.4 (encoded by *KCNJ5*) to form the acetylcholine-activated potassium channel ($I_{K_{ACh}}$ channel) with specific expression in the atrium. A mutant $I_{K_{ACh}}$ channel (*KCNJ3* p.N83H) is a cause of bradyarrhythmia, and can be effectively inhibited by NIP-151, a selective $I_{K_{ACh}}$ channel blocker. Thus, the $I_{K_{ACh}}$ channel might be considered to be a suitable pharmacological target, and genetic testing for genes such as *KCNJ3* and *KCNJ5* in patients with bradyarrhythmias may provide a drug treatment option.¹⁴

Indications for genetic testing are presented in Table 7.

Choice of the pacemaker mode

Several trials on patients with SSS and/or AV block, have compared atrial or dual-chamber with ventricular pacing.²⁰⁻²⁵ Although results have not been consistent, atrial-based pacing reduces the incidence of atrial fibrillation and may modestly reduce stroke compared to ventricular pacing, although it does not improve survival or reduce heart failure or cardiovascular death.²⁶ Ventricular desynchronization imposed by ventricular pacing even when AV synchrony is preserved, has been shown to increase the risk of heart failure and AF in patients with sinus nodal disease and normal baseline QRS duration.²⁷ DDDR pacing with a very short atrioventricular interval and more than 99% ventricular pacing has been reported to increase the incidence of atrial fibrillation, when compared with DDDR pacing with automated features to minimize ventricular pacing by prolonging the atrioventricular interval.²⁸ AAIR pacing has been associated with a higher incidence of paroxysmal AF and a two-fold increased risk of pacemaker reoperation compared to DDDR pacing programmed with a moderately prolonged atrioventricular interval,²⁰ whereas an AAI-DDD changeover mode had no effect on AF when compared with DDD.²⁹ Atrial antitachycardia pacing and managed ventricular pacing which minimizes unnecessary right ventricular pacing, has been found superior to conventional DDDR pacing by means of reducing AF in bradycardia patients,³⁰ but a convincing effect of overdrive atrial pacing or antitachycardia algorithms on reducing AF has not been documented in all trials.³¹ Low atrial septal pacing with dual-chamber pacemakers has been reported to reduce AF,³² but in the SAFE trial, pacing at the right atrial septum or continuous atrial overdrive pacing did not prevent the development of persistent AF in patients with paroxysmal AF and SND.³³ ***Bachmann bundle pacing*** is a new promising modality which theoretically might restore biatrial resynchronization and reduce atrial arrhythmias.^{34, 35} Atrial pacing, in general, appears to be arrhythmogenic.³⁶ Pacemaker mode selection is presented in Figures 5 and 6 and Table 8.

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