SYMPOSIUM
Cardiac Arrhythmias
(Part 3)

The Sick Sinus Syndrome

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SUMMARY
A review of the sick sinus syndrome (SSS) is presented stressing its multifaceted expressions, with slow and fast heart rates, syncopal and dizzy attacks, and rather vague nature early in its course. All ages are affected and the diagnosis must be considered if there is a modest degree of sinus bradycardia (SB), even if asymptomatic, as SB is less benign than was heretofore thought. Inappropriate or relatively slow sinus rates (RSSR) under stressful conditions are equally as important as SB. Inadequacy of the sinoatrial node (SAN) may be manifested by one or more of the following: (1) persistent severe and unexpected sinus bradycardia; (2) cessation of sinus rhythm (sinus arrest) for short intervals during which no other (escape) rhythm arises, or for somewhat longer periods with replacement of sinus rhythm by an atrial or junctional rhythm; (3) long periods of sinus arrest without the appearance of a new pacemaker and resulting in total cardiac arrest (ventricular arrhythmias may then follow); (4) chronic atrial fibrillation because the SAN is permanently silent, or repeated episodes of transitory atrial fibrillation due to total cessation of sinus rhythm at these times. Atrial fibrillation is often, but not always, accompanied by a slow ventricular rate (not produced by digitalis but resulting from an accompanying organic A-V block and the patient has binodal disease); (5) inability of the heart to resume sinus rhythm following cardioversion for atrial fibrillation (most likely if the ventricular rate is slow as mentioned above); and (6) episodes of sinoatrial exit block which are not related to drug therapy. These six items form the indirect evidences for the SSS and represent primary physiologic manifestations. Provocative tests are of value although not wholly satisfactory. Therapy for the chronic form will eventually be a ventricular artificial pacemaker. The natural history of the SSS is imperfectly known but probably covers 5–10 years, at least.

Additional Indexing Words:
Atrial disease  Sinus bradycardia  Sinus arrest  Sinus exit block  Sudden death
Atrial fibrillation  Syncope attacks

ALTHOUGH it was 67 years ago,¹ in 1906, that Flack, working during an elective period while still a medical student,² reported to Keith the first observation of the mammalian sinoatrial node (SAN), much about its function is unknown. To be sure, there are recent clarifications: its precise location; its size (circa 10 × 4 mm); its special centrally located arterial blood supply, with its artery branching from the right coronary artery in 55% of humans and from the left circumflex in 45%;³,⁴ its tripartite cellular population (pacemaker or P cells, transitional cells, and working myocardial cells);⁵ and the fact that there is more than one pacemaker cell or area at work in the SAN and that major changes in sinus rate result from suppression of one pacemaker site (or P cell) within the SAN and dominance of another, rather than a change in rate or intrinsic rhythmicity of the original pacemaker site.⁶ Electrophysiologic studies in animals have been numerous but such data are much more difficult to acquire in, or apply to, man. This is due primarily to the fact that even using intraatrial catheter electrodes the action potential of the SAN cannot be adequately recorded at any distance from

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this primary pacemaker site, and hence one must really impale the specialized tissue itself to secure the SAN spike. This has created an unsolved problem to date, and hence the primary generator function of the P cells in the SAN, as well as exit or entrance blockage between SAN and atrial cells, must be judged only indirectly. This is unfortunate since the dysfunctions of the SAN can, in all probability, be traced to these two basic types of nodal disorder.

Disease of the SAN is of increasing clinical import, and over the past few years a variety of clinical states have been recognized as pointing primarily to pathology of the human pacemaker; hence these conditions have been grouped together as the sick sinus syndrome. This syndrome appears not only in adults, in whom there is a wide etiologic spectrum, but also in children with congenital disorders and indeed probably explains a number of sudden deaths in children and young athletes. The fact that this potentially lethal sequence of events has escaped clinical recognition until recently is due to a number of reasons. Most important of these is the fact that sinus bradycardia has always been presented as essentially a benign condition, and the sick sinus syndrome (SSS) usually declares itself with this arrhythmia at its inception. Secondly, the multifaceted clinical expressions of the SSS beclouded the possibility of a single etiology until it was possible to collect continuous rhythm samples in patients with undiagnosed cardiac disorders and thus piece together what had seemed to be unrelated and separate cardiac arrhythmias.

Causes of Sinus Node Dysfunction

The basic disorders responsible for the events characterizing the SSS are, as mentioned above, sinus arrest (or generator failure) and/or sinoatrial exit block. While it is well known that vagotonia (either primary or due to digitalis) may produce these two effects, vagotonia as well as the effects of excessive potassium, quinidine, nicotine, beta-blocking agents, and aerosol propellants with fluorinated hydrocarbons is a transitory influence and not considered part of the SSS. Essentially the basic lesions are anatomic, with physiologic consequences which produce long-term disease, and can be seen in ischemic, sclerotic, rheumatic, and inflammatory conditions, as well as with acute or chronic coronary occlusions, pericarditis, cardiomyopathies, Friedreich's ataxia, progressive muscular dystrophy, collagen disease, surgical injury to the tissue, metastatic disease, infiltrative diseases of the atria such as amyloidosis and hemachromatosis, and as an isolated fibrotic local lesion of unknown cause. Familial sinus node disease without other illness has been found, as well as the familial syndrome of heritable Q-T interval prolongation with arrhythmias, syncope, and sudden death occasionally seen with congenital deafness, in which there is autopsy evidence of oblitative changes of the intranodal portion of the SAN artery with degenerative changes in the node.

The association of the SSS with myocardial infarction deserves special mention. Sinus node dysfunction occurs in about 5% of acute myocardial infarctions if monitoring is adequate. This dysfunction is suggested by sinus bradycardia and especially by transient junctional or atrial arrhythmias, notably atrial fibrillation, even if sinus arrest or sinus exit block is not seen. The sinus node has been found regularly to be infarcted in patients who develop atrial arrhythmias. Atrial infarction is exceedingly rare with isolated occlusions of the left anterior descending artery (which produces anteroseptal infarcts), and arrhythmias are not seen with disease of this vessel alone. In occlusions of the main right coronary artery and left circumflex, atrial damage is very common. This is expected since one or the other of these vessels provides the atrium and the SAN with its specific artery. Indeed SAN dysfunction can be expected in over half the patients with inferior infarcts. In one series, 31 of 32 patients with SAN disease had inferior infarcts. Anatomic disruption of the node has been implied so far, and in such cases pharmacologic intervention will often not succeed. However there are cholinergic terminals near the SAN and ischemia of these sites stimulates sinus bradycardia. Hence, in some instances of bradycardia in acute inferior myocardial infarction and such bradycardia is frequent in these infarcts), atropine may abolish the slow rate. Sinus node dysfunction usually appears within the first 4 days of the infarction and often is intermittently present at first, lasting only for an hour or so in some cases, indicating a dying node. The more prolonged manifestations of the SSS may supervene later. Thus patients who show SAN inadequacy during an acute infarction but recover this nodal function should have careful follow-up indefinitely. The more chronic stages, probably due to a slow fibrosis, may take several months or a few years to become permanent. If this possibility is overlooked, a late syncopal episode could be fatal.
Diagnosis of the Sick Sinus Syndrome

Ideally the diagnosis of dysfunction of the SAN should rest upon an analysis of alterations in the action potential of the pacemaker cells, for example duration, strength, duration and slope of phase 4 depolarization, and threshold potential, when generator failure is the root of the matter. If sinoatrial exit block is the problem, an analysis of the interval between the onset of the pacemaker action potential and the first atrial depolarization, or action potential, from the surrounding atrial myocardium or atrial specialized conduction fibers would reveal the delay and its characteristics. This sinoatrial conduction time has only been estimated in animals (for example 25-55 msec in the rabbit) and cannot be measured at all in man since as yet the action potentials from the SAN have not been recorded accurately. Since this latter is so, of course, definition of generator failure is similarly out of reach. The diagnosis of a failing sinus node therefore rests on indirect appraisals for the moment.

A further difficulty lies in the fact that dysfunction of the SAN may be intermittent and elude detection early in the illness. During apparently normal SAN behavior one must call on provocative testing of SAN function. Suspicion of a disordered SAN should arise particularly when one encounters sinus bradycardia, since this often initiates the disease.

Physiologic Manifestations

Inadequacy of the SAN may be manifested by one or more of the following: 1) persistent severe and unexpected sinus bradycardia; 2) cessation of sinus rhythm (sinus arrest) for short intervals during which no other (escape) rhythm arises, or for somewhat longer periods with replacement of sinus rhythm by an atrial or junctional rhythm; 3) long periods of sinus arrest without the appearance of a new pacemaker and resulting in total cardiac arrest (ventricular arrhythmias may then follow); 4) chronic atrial fibrillation because the SAN is permanently silent, or repeated episodes of transitory atrial fibrillation due to total cessation of sinus rhythm at these times. Atrial fibrillation is often, but not always, accompanied by a slow ventricular rate not produced by digitalis but resulting from an accompanying organic A-V block, and the patient has biventricular disease; 5) inability of the heart to resume sinus rhythm following cardioversion for atrial fibrillation (most likely if the ventricular rate is slow as mentioned above); and 6) episodes of SAN exit block which are not related to drug therapy. These six items form the indirect evidences for the SSS and represent primary physiologic manifestations. There may be other abnormalities associated with this syndrome, notably a relatively high incidence of A-V block and intraventricular conduction defects. It is also evident that in the bradycardic episodes in which no escape rhythm comes to the rescue, there is compromise also in the function of lower automatic centers (atrial or junctional). These extranodal involvements are probably a reflection of the extent of the basic pathologic process.

Evaluation of Sinus Bradycardia

The SSS often begins with sustained or periodic episodes of slow sinus rate. Hence the presence of sinus bradycardia (SB) in a symptomatic patient requires further evaluation (see below). Even in patients without overt symptoms, however, the assessment of SB may be necessary. More important is the fact that inappropriate sinus node rates also imply a failing SAN. For example, SB is present when rates are less than 55-60 beats/min. If a patient is seen in a clinical ambience where rapid sinus rates are expected, for example, with moderate acutely induced exercise, such as rapid arm or leg flexion for a few moments, severe pain, fever, or congestive failure, and the rate is inappropriately less, a relatively slow sinus rate (RSSR) is diagnosed and the SSS suspected. The vagal origin of many slow sinus rates is obvious, and thus SB or RSSR must be clarified further by their atropine response. It is urgent, however, to disseminate the concept that not all SB is benign. Another pitfall which may result in missing the SSS is the slow heart rate of the patient on digitalis. The first conclusion is usually that the rate is drug induced, and often this is correct. Especially in the aged, where the SSS is probably most common, "digitalis sensitivity" is assumed and the possibility of a dying SAN is not considered. It has become evident recently that in such individuals (those with the SSS) a reduction of dosage or elimination of the medication leaves the patients without a life-preserving inotropic effect. Thus they may die in chronic heart failure when they are treated only by artificially pacing the heart, while digitalis maintenance would solve the problem.

Use of Monitoring in the Diagnosis of Sick Sinus Syndrome

As can be seen by the manifestations of the SSS, the diagnosis of periodic sinus arrest with or
without escape rhythms, the mechanism of onset of paroxysmal atrial fibrillation or atrial tachycardia (i.e. its appearance as an escape mechanism after a long sinus pause), and sinus exit block all may require long-term observation by monitoring devices. At present the tapes available for use outside a hospital will sample 12-hour intervals and hence daytime and night periods must be employed. Both are needed, as it is often a surprise to find the SB or SA exit blocks arising during sleep. In one of our patients the sinus rate was 28 beats/min sleeping and 60 during the day. Obviously if syncopal attacks occur in constant relationship to certain events, these moments must be included. Posttachycardia sinus rates are very important in the suspected SSS and may be as slow as 25–35 beats/min for a short time and until the SAN warms up to a faster rate. This combination of tachycardias followed by SB (called by some the bradycardia-tachycardia syndrome) represents delayed SAN recovery time. This SAN overdrive suppression\(^{28, 24}\) can be used diagnostically by atrial pacing, if it does not appear spontaneously.

**Provocative Tests for the Sick Sinus Syndrome**

If monitoring devices are not of help, or cannot be used, certain provocations of sinus activity may uncover dysfunction or sluggishness. Atropine intravenously may reveal the vagal etiology of SB or exit blocks by eliminating them, or may greatly decrease postpacing sinus suppression, pointing to a cholinergic dominance and not the SSS. If intravenous atropine sulfate (1–2 mg) does not increase an SB to a sinus rate of over 90/min\(^{23}\) and if after atropine sinus node recovery time remains prolonged after overdrive (with atrial pacing at 120–140 beats/min for several minutes, usually 2–4) the diagnosis of a failing SAN is usually made. Intravenous isoproterenol can be tried as a SAN generator stimulus. One must avoid ventricular ectopic beats, if possible, by careful dose titration (1–2 mg/min). If the drug fails to whip the flagging SAN to fire above 90–100 beats/min this adds weight to the diagnosis. Atrial pacing is a valuable provocative maneuver, especially in the patient with a sick sinus in whom SB or exit block is not always present and the symptoms of the SSS are difficult to uncover. Atrial pacing with induction of a regular atrial tachycardia is probably a better challenge to SAN function than variably placed atrial premature depolarizations,\(^{29}\) and a sluggish SAN recovery time after atrial tachycardia, with or without escape rhythms appearing prior to resumption of sinus rhythm, is the best available indirect evidence for a failing SAN. The actual sinus node node recovery time after atrial pacing is related to the resting or control sinus rate, with slower control rates associated with longer maximum pauses.\(^{24}\) Overdrive suppression is seen in normal subjects as well as in subjects with SSS. In normal subjects the suppression is probably due to a reflex increase in parasympathetic tone.\(^{24}\) The diagnosis of the SSS rests upon the degree of overdrive suppression. This is best expressed as a percentage of the control rate,\(^{24}\) since in this way patients with the SSS in whom resting rates may be between 75 and 85 beats/min when tested can be evaluated. At such control rates the maximum pause in percentage change is between 115 and 128% of the control cycle length, or pauses of 800–900 msec. When the control rhythm is clearly a sinus bradycardia, with rates between 45 and 60, the maximum pause following atrial pacing is much longer, and the abnormal degree of postpacing suppression is easier to uncover. Pauses of 1200–1400 msec duration represent the critical figure beyond which abnormal suppression is diagnosed. At rates of 60 beats/min (a cycle time of 1000 msec) a pause of 125% of control (1250 msec) is strongly suggestive, and if pauses are longer this is probably diagnostic. At sinus rates of 45 beats/min (a cycle time of 1420 msec) a pause of 1700 msec or more is diagnostic even though the percentage increase is 120%. The maximum pauses in the SSS may be and often are much longer than this and may reach between 2000 and 6000 msec.\(^{23, 24}\)

Although atrial pacing remains the best indirect test of SAN activity, it has one pitfall. In the event that such pacing does not produce abnormal overdrive suppression (and the test would then be considered negative for the SSS) the possibility exists that it may be a false negative. An adequate challenge to the SAN by overdrive is based on the assumption that all of the rapid atrial depolarizations enter the SAN, i.e. that there is no sinoatrial node entrance block.\(^{25}\) Should there be such an impediment to depolarization of the SAN with each paced atrial beat, fewer such beats would enter (perhaps at a 2:1 or 3:1 atrionodal ratio), and the SAN would not be challenged at the same rate as the atrial myocardium. Thus in reality no overdrive would occur. There is no way as yet to obviate or discover such a possibility.

It is evident that none of the indirect tests, therefore, is wholly satisfactory, and much investigation of provocative maneuvers remains to be
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done. It is interesting clinically that as short a period as 15 sec of overdrive can result in substantial depression of SAN function.24 This postpacing pause may occasionally amount to 4-6 sec or more of asystole, which is equivalent to a ventricular rate of 15-10 beats/min. If such pauses are frequent and no lower pacemaker takes over, perfusion of vital organs will suffer.

Clinical Manifestations
The clinical expressions of disordered SAN activity can be multifaceted, intermittent, and even difficult to elicit. The basic physiologic defects center about hypoperfusion of the vital circulations, especially the brain, the heart, and the kidneys, as a consequence of sinus arrest, severe SB, or the rapid tachyarrhythmias which arise as escape manifestations following sinus pauses. Diminished cerebral arterial blood flow of a mild nature, particularly if periodic, can be cryptic, and one must be alert to slight personality changes such as irritability, fleeting memory losses, and nocturnal wakefulness, as well as to the more obvious changes such as slurred speech, pareses, errors of judgment, dizziness, and syncopal attacks. Often the patient himself has difficulty recalling such "spells" of lightheadedness or momentary lapses. Generalized body fatigue, muscle aching, mild digestive disorders (due to congestive phenomena and low cardiac output during periods of ventricular failure), modest and periodic oliguria, and fleeting pulse irregularities often called premature contractions may seem so vague a constellation of complaints that mild cardiac failure is overlooked. Periodic fulminating and unexplained episodes of acute pulmonary edema are now recognized as secondary to the SSS in some instances. Transitory but repetitive SB sets the stage for mild ventricular failure, especially if there is underlying coronary disease. Then the tachyarrhythmia, usually atrial fibrillation with rapid ventricular response or atrial tachycardia, follows and severe failure with pulmonary edema brings the patient to an emergency room. By this time the tachyarrhythmia may have ceased, and one finds a subject in severe respiratory distress with an inappropriately slow sinus mechanism (RSSR).

Unless the periodic bradycardia or arrest episode is perceived, it may take considerable time to arrive at a correct diagnosis of a chronically disordered and dying sinus node. A deceptive feature also is the fact that no other signs of heart disease may exist for some time unless one carefully searches the electrocardiogram. Evidences of the existent atrial disease can be seen in the abnormally wide P waves of intraatrial block, or when P waves change their shape, direction, or vectorial orientation, suggesting a new site of automaticity outside the failing SAN. The new atrial rhythm is seldom rapid and indeed fires at rates close to those of normal sinus rhythm. In these instances the atrial rate is usually slightly faster than that of the sluggish SAN, and the ectopic rhythm may be considered an escape phenomenon. Intraatrial block may precede symptomatic disease by several years.

The slow unfolding of the SSS is of course a chronic affair. The SSS can begin acutely, however, especially in myocardial infarction or sudden coronary insufficiency. In that event syncope, shock, pulmonary edema, or simply the symptoms associated with severe hypotension without shock are seen.

It is usual to find the chronic SSS in subjects of older age. However, as noted in several reports7, 9, 12, 21, 23 it also occurs in the young, age 11 and 13 years for example,7 as well as in every decade of life up to the 80s and involves both females and males. As James has noteda in the young athlete who died suddenly at age 18 years, vague symptoms had begun at age 13 when a RSSR went unappreciated. At age 14 years his heart rate was 42 beats/min and rose to only 70 beats/min on exercise. At 15½ years, he blacked out several times, and at 18 years he died while playing football. The deaf children with lesions in the SAN and prolonged Q-T intervals, and hence an increased duration of the ventricular vulnerable period,5, 6 appear to have syncope or death due to ventricular rather than atrial arrhythmias.

Therapy of the Sick Sinus Syndrome
From the provocative tests for the SSS it can soon be learned if atropine or isoproterenol can improve SAN function. These agents, however, are used in acute situations and are temporary aids since the treatment of choice is the insertion of an artificial demand pacemaker once chronic SSS is evident. Since associated A-V conduction system disease is not unusual,7, 21, 22 ventricular pacing is preferred. Should a patient refuse pacing and since chronic atropine or isoproterenol therapy is difficult, oral ephedrine can be tried. Probably at present, once the diagnosis of the SSS is made, one must consider a pacemaker in the near future for safety's sake, since the exact progress and timing of the

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complications of this condition are still unknown in great detail.

Course, Natural History, and Prognosis of the Sick Sinus Syndrome

Course

The sick sinus syndrome in its chronic form runs an erratic course with periods of normal node function alternating with abnormal behavior. This tends to cloud the homogeneity of the condition, allowing separated single and vague episodes to slip by undiagnosed correctly. Some of the signposts of note along the way are inappropriate heart rates, dizzy spells, episodes tagged as convulsive disorders in the young, especially unexplained episodes of congestive failure, and finally syncopal or cardiac arrest attacks. Periodic or sustained SB can no longer go unchallenged even if asymptomatic and is a major evidence of this disorder in its early stage. Paroxysmal atrial fibrillation without evident heart disease may be another signal to explore the behavior of the SAN. Since the provocative tests are not difficult to perform, such exploration must now be done in increasing numbers.

Natural History

The natural history of this syndrome of disordered SAN function is only just now becoming apparent as the varied episodes are gathered together under one etiology. The knowledge is far from complete, but at present it appears that the SAN may die quite slowly, taking 5–10 years or more to cease functioning completely. Sinus bradycardia may progress to various forms of exit block or may simply become increasingly severe until no sinus beats are found. The escape rhythms, at first only periodic rescuers, eventually become the basic mechanism, particularly atrial fibrillation. When the latter exists with a slow ventricular rate in an undigitalized subject it is probably an end stage of SAN disease. Between these extremes of the SSS there may be many different physiologic adjustments. Because of this one would like to predict the crucial time for insertion of a pacemaker, since atrial fibrillation is probably the only stable long-term replacement rhythm and is not always the escape rhythm to arise. Other less stable escape rhythms often fail to fire after a while, especially if the disease process itself progresses to involve these other specialized tissues (junctional, atrial). Unfortunately such a prediction is not yet possible. The deterioration of SAN dysfunction may proceed slowly at first then speed up and produce a disastrous asystole or some other marked change in the patient. Such was the case in a 71-year-old female diabetic with arteriosclerotic peripheral vascular disease whose SSS began 6 years before she needed a pacemaker. Undiagnosed at first, she had had a pulse rate of 60–65 beats/min at a time when occlusion of her left brachial artery caused three fingers of her left hand to necrose. The excruciating pain did not yield even to large doses of morphine, and heart rates nearer to 90 beats/min would be expected. Once the fingers were amputated and the vessel occlusion surgically relieved, pain ceased and her pulse dropped into the mid-50s. During the next 4 years she grew more tired and forgetful. Then in the 2 years before being seen in our hospital she had four episodes of severe pulmonary edema. Each time she had a slow sinus rate when she was seen in an intensive care unit, and only once was atrial fibrillation (with a ventricular rate of 150–160 beats/min) demonstrated before a return to SB. She was digitalized once and then this was stopped due to slow resting sinus rates (45–54 beats/min). She was admitted to our hospital for diagnosis of the cause of the repeated pulmonary edema. The SB was tested with atropine, isoproterenol, and atrial pacing, and the tests were all positive. She was redigitalized and sent home in the hope that the drug would block the rapid ventricular rate when she developed atrial fibrillation. Digitalization did not alter her SB, which one hoped would not slow further at home. However, 3 months later her electrocardiogram demonstrated complete sinus arrest and an unstable junctional rhythm at 30–40 beats/min. An artificial pacemaker was immediately installed, and she has felt very much better with a regular rate of 70 beats/min and has had no failure or fibrillation.

Prognosis

The long-term prognosis of the SSS cannot be stated with certainty in any one case since the end stage of sinus arrest cannot be predicted. However, since asystole can occur periodically and congestive failure can result also, the outcome is likely to be poor eventually. It does not appear likely that the failing SAN can be cured, at least with present therapies. Hence replacement of its function by a demand pacemaker is inevitable in most patients. If this intervention with all its problems is accepted by the patient, one may never fully know the natural history of the untreated SSS and hence prognosis will also be relatively uncertain. Time and careful
observation of these patients will provide us with further information.

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