Congenital Sick Sinus Syndrome With Atrial Inexcitability and Coronary Sinus Flutter

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Congenital sick sinus syndrome has been described sporadically. The syndrome may comprise various components of sinus bradycardia, atrial fibrillation, and right atrial inexcitability.1–7 In the current case, detailed electrophysiological evaluation was undertaken with electroanatomic mapping of the right atrium and coronary sinus (CS) and of associated supraventricular arrhythmias.

Case
A 37-year-old asymptomatic male physician from Mexico without any previous medical problems was referred after routine physical examination for evaluation of atrial fibrillation with a slow ventricular rate. Arrhythmia duration was unknown. He stated that bradycardia had been consistently noted on previous clinical examinations and had been attributed to competitive long-distance running since childhood. Heart rates in the “40s” had been noted since age 10 to 11 years when he had been informed of a “heart murmur.” Subsequent echocardiographic examination had been normal. The patient denied any family history of sudden death or arrhythmias. He had no siblings and no children. His prior records (and those of his parents) were unavailable.

Physical examination was normal except for a regular bradycardia of 45 beats/min. Twelve-lead ECG showed fixed R-R intervals. No clear P-wave activity was identified. However, there was small-amplitude baseline electric activity of debatable origin, interpreted variously by experienced electrocardiographers as standstill, artifact, or atrial fibrillation waves (Figure 1A). A transthoracic echocardiogram showed normal ventricular volume and function (left ventricle end-diastolic diameter, 52 mm; left ventricle end-systolic diameter, 34 mm) and mild tricuspid regurgitation with estimated pulmonary artery systolic pressure of 40 mm Hg. Baseline atrial activity (if any) was not interpretable because of exercise artifact. Isolated premature ventricular contractions were observed during exercise. A 24-hour Holter monitor showed regular rhythm (mean heart rate, 47 beats/min; range, 35–95 beats/min; maximum R-R interval, 1.8 s) with 56 ventricular bigeminal cycles. The only symptom during recording periods was an abnormal lateral chest sensation that corresponded with heart rates between 30 and 40 beats/min. The patient underwent an external cardioversion without appreciable change in heart rate (44 beats/min), although electrocardiographic intervals between QRS-T complexes became completely isoelectric for several minutes before small-amplitude deflections resumed (Figure 1B).

At electrophysiology study, the first electrode catheter was placed in the CS and demonstrated regular, rapid atrial activity at a cycle length of 274 ms, suggestive of atrial flutter (Figure 3A). In striking contrast, a subsequently placed duodecapolar electrode catheter sited conventionally to map the right atrial free wall and cavotricuspid annulus recorded no electric activity, despite excellent tissue contact. This remained unchanged by deflecting the catheter around the right atrium to include posterior locations or by varying its vertical tilt. Point-by-point electroanatomical mapping (CARTO) confirmed absolute lack of recordable electrograms in the free wall (Figure 4A through 4C). Low-voltage activity was observed in the septum at and above the ostium of the CS. Normal CS electrograms were recorded in the body of the CS but diminished distally. Exploration of the anticipated region of the sinus node (filter settings, 0.05–500 Hz) revealed slow (<30 beats/min) electric activity in a discrete location without corresponding local atrial depolarization (Figure 4D).

Atrial flutter was mapped to a region of the proximal CS and its roof. Fractionated local electrograms were recorded at its junction with the inferior midseptum. Flutter was not pace terminable. Radiofrequency energy applied to the proximal CS slowed tachycardia and rendered it pace terminable. On termination, the His bundle escape rhythm was clear (Figure 3C). The His-ventricular interval (50 ms) was normal. An irregular, dissociated slow atrial escape emerged from the distal CS. No AV or VA conduction was observed with CS or...
ventricular pacing. The junctional rhythm was remarkably responsive to isoproterenol, increasing to 130 beats/min at a dose of 1 μg/kg per minute, and easily suppressible by ventricular pacing, which resulted in offset pauses of up to 4 s. Attempts at right atrial stimulation were unsuccessful, despite using high outputs (20 mA and 9-ms pulse widths) at various sites. Inexcitability of this chamber was absolute. More aggressive ablation attempts were not made in the junction of CS roof and midseptal area to avoid potential injury to junctional activity, that is, the source of this patient’s intrinsic rhythm. Fibrillatory activity spontaneously occurred in the CS (Figure 3D).

Ventricular effective refractory periods were normal. A single-chamber permanent pacemaker was recommended and implanted, and anticoagulation with warfarin initiated. Twelve-lead ECGs during follow-up showed variability. Asymptomatic corrected QT interval prolongation was intermittently observed (Figure 1). Genomic DNA was isolated from blood, and polymerase chain reaction was used to amplify the coding region and flanking intronic sequence of SCN5A as previously described. Sequencing reactions were performed in the presence of fluorescent-labeled dideoxynucleotides and additional primer for exon-specific sequencing in both sense and antisense direction on isolated polymerase chain reaction product. SCN5A was evaluated as a candidate gene, and mutations were sought using direct, bidirectional sequencing of the coding region. Sequence analysis revealed a heterozygous change of adenine to guanine (A1673G), resulting in an amino acid change from histidine to arginine (H558R) at codon 558, a common SCN5A polymorphism.

Discussion
A spectrum of asymptomatic electrophysiological abnormalities of sinus node, atrial excitability, and ventricular repolarization was observed in the current case. These features are consistent with the syndrome of congenital absence of the sinus node that has been sporadically reported over several decades. Abnormalities may extend beyond the sinus node mechanism and incorporate various additional elements of atrial refractoriness, flutter, or fibrillation-like supraventricular activity; familial carriage; and sudden death. There may be an association with cardiomyopathy. To our knowledge, the current case is the first detailed electrophysiological assessment of this condition.

The occurrence of sinus node dysfunction and atrial arrhythmias in young patients is puzzling. In adults, the combination is well described and may represent effects of aging and comorbidities, such as hypertension, coronary artery disease, and LA fibrotic disease. In young patients, prior structural heart disease or surgery may predispose similarly. In contrast, the current case describes isolated sick
sinus syndrome. This rare condition also has sometimes been associated with difficulty in atrial pacing. Pathological data are scant. In one case, open chest device implant (for sudden death) permitted direct visualization. Atria, which had been inexcitable and devoid of electrogram activity during prior EP study, appeared glistening white, compatible with complete fibrotic replacement (P. Tchou, MD, personal communication, July 2011). Histology may reveal myocardial fibrillar disarray, degeneration, and interstitial fibrosis. In 2 patients with congenital sinus node disease who died suddenly, atrophy, degeneration, and isolation of the sinus node with fatty metamorphosis of the atrial preferential fibers that approach the sinoatrial node was noted. More recently, several genetic lesions have been described in association with this syndrome.14

In the current case, isolated sinus node activity was detected during endocardial mapping (Figure 4D). In normal patients, electrode catheter recording in the sinus node region demonstrates cyclic activity with slowly rising low-amplitude deflections.15,16 These endocardial extracellular recordings, similar to those recorded experimentally with intracellular electrodes, are consistent with sinus node depolarizations. Normally, each is followed closely by the higher-frequency larger-amplitude deflection of local atrial depolarization. When absent (eg, in second-degree sinoatrial block), the smooth descending contour of the sinus node electrogram may be revealed.15 In the current case, the recording of periodic electrograms indicated the presence of sinus node pacemaking activity, although this was very slow; however, these were never accompanied by atrial depolarization, indicating permanent sinoatrial conduction block.

Electric activity was conspicuously lacking throughout the right atrial body. The chamber did not depolarize in response to CS electric activity (fibrillation, flutter, ectopic rhythm, or pacing) and remained inexcitable during direct high-current stimulation. Electric inexcitability was accompanied by mechanical standstill. Right atrial electric abnormality has been described previously in conjunction with congenital sick sinus syndrome, manifesting with prolonged effective refractory periods or more severely with complete inexcitability, and likely underlies the inability to find a suitable atrial electrode position during attempted permanent pacing. This range of abnormality may represent a natural history, that is, earlier subtle electrophysiological abnormalities progressing to complete inexcitability by young adulthood. Mapping in the current case demonstrated that inexcitability was not a regional phenomenon but extended throughout the chamber. This supports a primary electric abnormality and not the consequence of a secondary process (eg, postsurgery) when regions of preserved function mingle with scarred and fibrotic tissues.

The left atrium was likely affected similarly to the right atrium for the following reasons. Normally, the CS musculature is electrically connected to both the right and left atria.

Figure 2. Transthoracic echocardiographic examination of the tricuspid (left) and mitral valve (right). The top shows Doppler echocardiography of mitral and tricuspid inflow. Normally during diastole, an E wave representing early diastolic filling is followed by an A wave of late diastolic filling propelled by atrial contraction. In this case, the E wave is present, but the A wave is absent, indicating an absence of both left and right atrial contraction. The bottom shows pulsed tissue Doppler echocardiography of mitral and tricuspid annuli. E', representing early diastolic recoil, is observed in both tricuspid and mitral annuli. E' velocities are normal, consistent with normal diastolic relaxation. However, A' velocities are absent, confirming lack of both left and right atrial contractile activity.
Electrograms recorded from the proximal CS represent composite effects of depolarization both of the left atrium, a rounded, low-frequency potential, and of the CS musculature, characterized by a sharp potential. However, in the current case, electrograms inscribed in this region were characteristic of CS musculature only and lacked the low-amplitude far-field components of left atrial activity seen normally. Surface ECG inscription of atrial activation, normally dominated by depolarization of the comparatively massive left atrium, is distorted and diminished by scar replacement. Here, the failure of CS rhythms (flutter or ectopic rhythm) or pacing to inscribe significant surface P waves supported left atrial electric abnormality. Surface ECG inscription of atrial activation, normally dominated by depolarization of the comparatively massive left atrium, is distorted and diminished by scar replacement. Here, the failure of CS rhythms (flutter or ectopic rhythm) or pacing to inscribe significant surface P waves supported left atrial electric abnormality. Echocardiographically, the right and left atria were affected similarly (ie, demonstrated enlargement and mechanical standstill) (Figure 2). Increased left atrial pressure has been noted on invasive hemodynamic measurements in a prior study. These observations indicate that inexcitability and standstill are likely common to both atrial chambers in this syndrome, although definitive demonstration would require direct left atrial mapping. This form of atrial pathology may increase propensity to thrombus formation, similarly to fibrillating atria, even without conventional CHADS (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and prior stroke) risk factors.

Atrial fibrillation has been associated with congenital sick sinus syndrome. The presence of atrial inexcitability would appear to be incompatible with (and indeed preclude) the coexistence of fibrillatory effect. In some instances, atrial standstill may be misinterpreted as fibrillation on a surface ECG. Some previous reports attributed the source of flutter and fibrillation-like phenomena to the tricuspid valve or within the His bundle to explain how part of the atrium can be in atrial flutter despite electric standstill elsewhere in the same chamber. The current case with detailed mapping may reconcile these findings. The CS acted as a distinct nonatrial source of supraventricular arrhythmias. The CS is intimately connected with both atria but derives separate embryologically origins from the left sinus horn and contains myocardial fibers. The muscular sleeve is known to participate in flutter circuits and in the maintenance of atrial fibrillation.
through its left atrial connections. Elimination of the latter may be an objective during atrial fibrillation ablation.\textsuperscript{22,23} In the present case, the CS was anatomically and electrically normal but electrically “isolated” because atrial connections, if existent, led to an inert chamber. This supports the notion that the muscular CS per se can contain flutter circuits and sustain fibrillatory activity without any atrial contribution, despite its lesser muscular bulk. These may explain the diminutive surface ECG inscription of "flutter waves" and the response to cardioversion (Figure 1). These sustained arrhythmias may be triggered by ectopic activity from cells with pacemaker activity in the CS and vein of Marshall.\textsuperscript{24,25} The terminal portion of the muscular CS connects with the right atrium\textsuperscript{21} and produces fibers extending anterosuperiorly into the interatrial septum close to the AV node.\textsuperscript{22,24} It is possible that these extensions, interlacing with inexcitable tissues, were responsible for some degree of voltage preservation observed inferior to the point of inscription of the His electrogram (Figure 4).

Normally, the AV node receives left- as well as right-sided inputs. The observation that CS pacing normally results in shorter AH intervals compared with right atrial pacing may signify that the CS has a preferential input bypassing a section of the AV node.\textsuperscript{26–28} However, in the current case, there was no AV conduction associated with CS rhythm (Figure 3B), indicating that the CS did not maintain an independent direct AV nodal connection.\textsuperscript{17} An AV nodal escape rhythm is characteristic of this condition (Online Mendelian Inheritance of Man database [OMIM] 163800).\textsuperscript{29} The current patient had a robust escape and remained asymptomatic until incidental discovery. However, an association with syncope and sudden death indicates that the syndrome may not always be benign.\textsuperscript{1,11,30} This could result from inconsistencies in the junctional escape rhythm responsible

Figure 4. Electroanatomic mapping of the right atrium and CS (A through D, reading counterclockwise). A through C, Bipolar chamber mapping was performed using a CARTO 3D electroanatomical mapping system. Areas are color-coded according to electrogram voltage recorded (red, \(<0.10\) mV [scar]; violet, \(>0.5\) mV [normal]; intermediate colors, 0.1 to 0.5 mV [representing transitional zones]). Dots signify recording points (silver, areas mapped for sinus node activity; orange, sites recording His bundle depolarization; red, ablation lesion locations). A, RAO projection. B, Left posterior oblique (135°) projection. Electrograms with voltage in the transitional range were observed over the midseptum at the margins of the CS. Ablation lesion locations are marked in the low midseptal region. C, LAO projection showing the CS extending to its junction with the great cardiac vein and His bundle inscription. CS voltages are normal. D, The anticipated zone of the sinus node in the superior vena cava-right atrial junction was explored using unipolar map settings (0.05–500 Hz) marked by silver dots in A through C. Electric recording at the superior vena cava-right atrial junction (marked by arrow in A) shows cyclic electric activity (~3000 ms), suggesting sinus node electrograms (marked by arrows in D) (see Discussion). Concurrent CS recordings display rapid supraventricular arrhythmia. CS indicates coronary sinus; LAO, left anterior oblique; RAO, right anterior oblique.
for sustaining ventricular activity. In the current case, intermittent ventricular repolarization abnormalities indicated extension of electric pathology beyond atrial tissue, possibly predisposing to ventricular arrhythmias, and this may be an additional cause of syncope and sudden death in this condition.

One or more underlying ion channel defects likely explain this condition, with familial clustering and effects spanning the entire cardiac electric cycle from sinus node depolarization to ventricular repolarization.2,7,14,29–31 Mutations in the gene for the cardiac Na+ channel (SCN5A)32–35 have been implicated, although sinus pacemaker activity does not require Na+ channel activity. One explanation proposed for this is a failure of conduction of impulses from the sinus node to the adjacent atrial myocardium rather than an electric lesion of the sinus node itself. The current case is the first in our knowledge to directly test and provide support for this hypothesis because sinus node electromgrams could be recorded in isolation without evidence of local atrial depolarization (Figure 4D). Nevertheless, sinus node activity was slow. Therefore, we cannot assert that sinus node function was normal but disguised by atrial inexcitability. The findings also indicate the balance of dynamic processes affecting both the sinus node and atrial excitability. Thus, carriers of recessive SCN5A mutations may demonstrate initial sinus bradycardia but atrial inexcitability later in life.32 An inherent disorder of the sinus node is supported by the observation that sinus bradycardia is frequently found in carriers of dominant long-QT 3 mutations.14 Other genes also may play a role (eg, HCN4 in idiopathic sinoatrial node disease36) and in individuals with the combination of long QT, ventricular tachycardia, and sinoatrial node disease.37 Mutations in a Ca2+-handling gene (calsequestrin gene, CASQ2) that lead to autosomal recessive catecholaminergic polymorphic ventricular tachycardia also are associated with sinoatrial node dysfunction,37 and some patients have revealed a right bundle branch block with a Brugada-like ST-segment elevation. The phenotype of atrial standstill may be accompanied by connexin40 abnormalities.74–38 Multiple clinical arrhythmia phenotypes (sinus node dysfunction, atrial fibrillation, ventricular arrhythmias) suggest involvement of complex molecular phenotypes in each individual cardiac cell type, and these require further elucidation.

In conclusion, this congenital electric disorder was dominated by atrial inexcitability with ensuing loss of electric connectivity to adjoining structures (ie, the sinus and AV nodes and CS) and was not merely an isolated disorder of sinus pacemaker cells. Although historically described as congenital sick sinus syndrome, this term may be a misnomer because it incompletely describes frequently accompanying electric abnormalities in the ventricular myocardium and conduction system in addition to genetic ablation of atrial excitability.

Disclosures
None.

References
The case presentation by Varma et al brings to light the importance of appreciating varying arrhythmias in separate portions of the atrium in an exceptional situation—a patient with a sodium channel mutation affecting sinus node function and atrial conduction. These findings, however, bring into focus critical issues in terms of mapping and understanding multiple arrhythmias simultaneously but in isolated (partially or completely) portions of the atria and coronary sinus. These findings also underscore the importance of considering the atria as electrically independent chambers rather than a single continuous structure. This approach is particularly relevant in the context of congenital atrial standstill, which is characterized by the absence of sinus rhythm and the presence of multiple atrial standstill rhythms in different parts of the atrium.

The arrhythmia may be contained within this cardiac chamber in exceptional cases. The atrial standstill rhythm anomalies: clinical and pathological correlations. Pacing Clin Electrophysiol. 1992;15:1720–1729.


EDITOR’S PERSPECTIVE

In this segment of Teaching Rounds in Cardiac Electrophysiology, Varma et al present and discuss an interesting patient with an electrically silent right atrium but with supraventricular arrhythmia rising within the coronary sinus. There are several teaching points of value that are highlighted by this case and discussion for the interventional electrophysiologist. Intratrial segmentation and dissociation. As we perform increasingly complex ablation procedures in patients with prior maze procedure, multiple atriotomies, congenital heart disease, and so forth, we now appreciate that the atria cannot always be considered as 1 electrically continuous complete structure. Patients may have 2 different rhythms (sinus and atrial fibrillation, atrial flutter, or atrial fibrillation) in the right and left atria. When the atria are truly dissociated from each other, each chamber’s arrhythmia can be addressed independently. More complex scenarios occur when the 2 atria are not electrically disparate structures; rather, varying degrees of entrance and exit block between them are present. In such cases, mapping of the arrhythmia (flutter in the right atrium when there is variable conduction into the right atrium from rapid tachycardia in the left atrium) is necessary. The more rapid or disorganized arrhythmia will need to be terminated with pacing or cardioversion and then the slower arrhythmia induced in the chamber of origin mapped and ablated. The coronary sinus as a distinct chamber. Electrophysiologists now accept that the coronary sinus represents a fifth cardiac chamber with its own atrial myocardium and venular tissue. This chamber may show in patients an independent arrhythmia or serve as a conduit between the atria for large loops of interatrial reentrant tachycardia as highlighted in this present case. The arrhythmia may be contained within this cardiac chamber in exceptional cases.

What will be our reference point? In addition to difficulty with simply mapping 1 chamber’s arrhythmia when another chamber or segmented portion of the atrium has another arrhythmia, picking the reference electrogram to create an activation map can be challenging. For example, in a patient with congenital heart disease, prior atriotomy, and a right-sided maze procedure, it is not uncommon to find an isolated portion of atrium on the free wall with a cycle length of activation different from a flutter in the remaining right atrium or left atrium. If the same reference for mapping is used, then taking activation points in the isolated chamber will create a meaningless map that cannot be used to define the circuit or ablation targets in either of these portions of the atrium. The electrophysiologist will need to create separate maps, each with its own reference point located within the portion of the atrium being mapped.

The case presentation by Varma et al brings to light the importance of appreciating varying arrhythmias in separate portions of the atrium in an exceptional situation—a patient with a sodium channel mutation affecting sinus node function and atrial conduction. These findings, however, bring into focus critical issues in terms of mapping and understanding multiple arrhythmias when occurring simultaneously but in isolated (partially or completely) portions of the atria and coronary sinus.
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