 Persistent sinus nodal electrograms during abnormally prolonged postpacing atrial pauses in sick sinus syndrome in humans: sinoatrial block vs overdrive suppression


ABSTRACT A transvenous electrode catheter technique was used for direct recording of bipolar sinus node electrograms during postpacing atrial pauses. Multiple repetitive local sinus node electrograms during atrial quiescence validate sinus node electrograms. Such atrial pauses with sinus node electrograms are due to sinoatrial block; atrial pauses without sinus node electrograms are due to overdrive suppression or improper recording. Eight consecutive patients were prospectively selected on the basis of a corrected sinus node recovery time greater than 1500 msec during diagnostic electrophysiologic evaluation. Six patients had atrial pauses with sinus node electrograms; three patterns of sinus node electrograms during atrial pauses were observed. We conclude that (1) sinus node electrogram recording is of value in understanding the mechanism underlying postpacing atrial pauses; (2) atrial pauses are usually (6/8) caused by sinoatrial block; (3) three patterns of sinus node electrograms are observed, thus making indirect interpretation unreliable.

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RECENT STUDIES, both experimental and clinical, report the feasibility of recording an extracellular sinus node electrogram with a conventional transvenous electrode catheter technique.

Experimental proof for the validity of sinus node electrograms was provided by simultaneously recording the transmembrane action potential and the extracellular potential of the sinus node and by inducing sinus nodal exit block with tetrodotoxin (TTX). The clinical evidence is more indirect and relies on the temporal relationship of the sinus node electrogram to the P wave and its similarity to the waveform recorded experimentally.

We reasoned that if the periods of atrial quiescence were sufficiently long, we could record multiple, repetitive, isolated sinus node electrograms. This recording, which is possible in the long atrial pauses observed after pacing in patients with sick sinus syndrome, would corroborate the existing evidence and establish sinoatrial block instead of overdrive suppression as the mechanism underlying the pauses.

Materials and methods

Patients. Among patients referred for diagnostic electrophysiologic evaluation, eight (table 1) were prospectively selected on the basis of a corrected sinus nodal recovery time (CSNRT) in excess of 1500 msec; this limit was chosen because it is clearly abnormal and encompasses several basic cycle lengths (BCLs), a requisite for identification of repetitive sinus node electrograms. Pertinent clinical features are summarized in table 1. Each patient gave informed consent and no patient was on medication before the electrophysiologic study. However, patients 2 and 3 were given ajmaline (1 mg/kg iv over 1 min) during the diagnostic procedure. The CSNRT of patient 2 was not modified by the administration of the drug. Patient 3 had a normal CSNRT before ajmaline was injected and developed spontaneous sinoatrial block and an abnormal CSNRT after the drug was injected.

Electrophysiologic studies. At the end of the routine diagnostic protocol, the right ventricular catheter was replaced with a bipolar catheter electrode (No. 7F; 1 to 1.5 cm interelectrode distance, guide wire) that was carefully looped over the node (Berzin et al., submitted for publication). The criteria used to localize the node were both anatomic (distal electrode at the junction between the superior vena cava and the high right atrium as judged from biplane fluoroscopy) and electrophysiologic (lowest site of exclusive atrial negativity). The polarity of the bipolar sinus lead was reversed to obtain upward atrial
TABLE 1
Clinical and electrophysiologic characteristics

<table>
<thead>
<tr>
<th>Patient No./sex</th>
<th>Age (yr)</th>
<th>Symptoms</th>
<th>ECG</th>
<th>BCL (msec)</th>
<th>CSNRT (msec)</th>
<th>Pn</th>
<th>Amplitude (msec)</th>
<th>Duration (msec)</th>
<th>Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M 29</td>
<td>None</td>
<td>ISB IJR</td>
<td>720-840</td>
<td>4,560 f</td>
<td></td>
<td>5</td>
<td>6</td>
<td>20</td>
<td>440-600 1</td>
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<tr>
<td>2/F 82</td>
<td>Syncope</td>
<td>NSR</td>
<td>600</td>
<td>1,760 S</td>
<td>(420 f)</td>
<td>3</td>
<td>3</td>
<td>30</td>
<td>300-400 2</td>
</tr>
<tr>
<td>3/F 70</td>
<td>Presyncope</td>
<td>NSR</td>
<td>700-820</td>
<td>7,600 f</td>
<td></td>
<td>9</td>
<td>9</td>
<td>25</td>
<td>250-360 1-3</td>
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<tr>
<td>4/F 70</td>
<td>Presyncope</td>
<td>ISB</td>
<td>740-800</td>
<td>5,000 S</td>
<td></td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5/F 74</td>
<td>Presyncope</td>
<td>IJR</td>
<td>780-860</td>
<td>5,350 f</td>
<td></td>
<td>0</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>6/F 63</td>
<td>Presyncope</td>
<td>2:1 SAB</td>
<td>700-800</td>
<td>5,620 f</td>
<td></td>
<td>5</td>
<td>7</td>
<td>12</td>
<td>280-400 2</td>
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<td>ISB</td>
<td>1000</td>
<td>&gt;21,220 S</td>
<td></td>
<td>26</td>
<td>&gt;5</td>
<td>17</td>
<td>450 1</td>
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<tr>
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<td>Presyncope</td>
<td>IJR</td>
<td>630-680</td>
<td>4,130 S</td>
<td></td>
<td>9</td>
<td>5</td>
<td>10</td>
<td>400-420 2</td>
</tr>
</tbody>
</table>

ISB = intermittent sinus bradycardia; IJR = intermittent junctional rhythm; SAB = sinoatrial block; f = first postpacing cycle; S = secondary pause; Pn = number of pauses adequate for analysis; SNE = sinus nodal electrogram; n = maximum number in a pause; NSR = normal sinus rhythm.

*For further information, see Results, description of figure 4.

Deflections. High amplification (up to 0.02 mV/cm) was used and filter settings were 0.5 to 30 Hz. Multiple peripheral electrocardiogram (ECG) leads and a high right atrium lead were simultaneously recorded both on a multichannel oscilloscopic photographic recorder (Electronics for Medicine VR 12) and on a direct ink jet recorder (Elema Schönander Mingograf 8000) at a paper speed of 25 to 100 mm/sec. Rapid atrial pacing (Janssen programmable digital stimulator; twice diastolic threshold, 2 msec duration) was induced for 1 min sequences and the ensuing pauses were recorded. Fine adjustments in catheter position were then made until sinus node electrograms were obtained. Negative pauses, i.e., atrial pauses without sinus node electrograms, are due to sinus arrest (overdrive suppression) or improper recording. In patients 7 and 8, baseline drift proved to be a major technical problem at low filter settings. After clear visualization of discrete sinus node electrograms at filter settings of 0.5 to 30 Hz, the filters were set at 1 to 30 Hz to decrease baseline drift, thus allowing a stable recording of the sinus lead in these two patients. The results are internally consistent in that all pauses (either a first postspacing cycle or a secondary pause) in each patient are either positive (i.e., with sinus node electrograms) or negative once the best location and amplification are found. Three to 26 pauses (table 1) are analyzed for each patient.

Definition of terms and criteria for interpretation. The criteria for validation consist of recording multiple, identical, repetitive, low frequency, local (i.e., confined to the sinus lead) deflections during atrial quiescence on both high right atrium and ECG leads. These features are observed experimentally after TTX administration and no artifact is known to be capable of producing them. The localization of sinus node electrograms is based on both sequential and simultaneous high right atrium recordings. Once the catheter is looped correctly as judged from fluoroscopy, negative pauses are first recorded in each patient (0.5 to 30 Hz, high amplification). Careful exploration of the anterior aspect of the junction between the superior vena cava and the right atrium is necessary to select the limited area with positive pauses; positional accuracy of a few millimeters proves critical. Simultaneous recording of a high right atrium lead with the same filters (0.5 to 30 Hz), either from a catheter free in the lumen of the junction or against the high intratral septum, confirms the absence of sinus node electrograms.

Positive pauses are assumed to be caused by sinoatrial block because they do not fit into the classic overdrive suppression theory, and in the experimental setting their causal mechanism is the exit block. Therefore a relationship of the intersinus node electrogram cycle length to the BCL is expected. Sinus node electrograms are first validated according to the above criteria and then three different patterns of sinus node electrograms are described.

Results

Negative pauses. Patients 4 and 5 had negative pauses; no sinus node electrograms were recorded. Incomplete exploration may be responsible for the recording failure, although obviously overdrive suppression cannot be excluded.

Positive pauses: sinus node electrogram validation. Figures 1 to 5 illustrate the application of the criteria for validation. Figure 1 depicts data from patient 3. During two spontaneous pauses, one and then four isolated identical deflections are clearly seen in the low-frequency sinus lead during atrial quiescence. The intersinus node electrogram cycle length (780 to 920 msec) approximates the BCL (700 to 820 msec); electrical activity is continuous with a slow diastolic slope between sinus node electrograms. Similar deflections are noted during postpacing pauses (figures 7 and 10, first postspacing cycles).

Figure 2 depicts data from patient 2. Three isolated identical deflections are clearly seen, restricted to the low-frequency sinus lead during atrial quiescence (secondary pause). The sinus lead activity is continuous with a slow diastolic slope merging with the sinus node
electrograms. Figures 8 and 9 depict data from the same patient.

Figure 3 depicts data from patient 6. Seven deflections are restricted to the low-frequency sinus lead during atrial quiescence (first postpacing cycle). The intersinus node electrogram cycle length (740 to 800 msec) approximates the BCL (700 to 800 msec); electrical activity is continuous with a slow diastolic slope between sinus node electrograms.

Figure 4 depicts data from patient 7. Five deflections are restricted to the low-frequency sinus lead during atrial quiescence (secondary pause). The appearance of a slow junctional escape rhythm without retrograde conduction to the atria allowed 20 more sinus node electrograms to be traced before resumption of atrial activation. The intersinus node electrogram cycle length (950 to 1090 msec) approximates the BCL (1000 msec) and electrical activity is continuous.

Figure 5 depicts data from patient 8. Three deflections are restricted to the low-frequency sinus lead during atrial quiescence (secondary pause). The intersinus node electrogram cycle length (650 msec) equals the BCL (630 to 680 msec) and electrical activity is continuous. The first atrial depolarization after the pause is a typical dominant pacemaker pattern (slow diastolic slope, slow upstroke, and fast atrial deflection) that is much less conspicuous in the following beats despite a constant BCL (shorter sinoatrial conduction time and/or pacemaker shift).

Figure 6 depicts data from patient 1. Four deflections are seen in the low-frequency sinus lead during atrial quiescence (first postpacing cycle).

Positive pauses: sinus node electrogram patterns. Three patterns of sinus node electrograms are observed during these long pauses. The escape intervals between
the last paced atrial beat and the first isolated sinus node electrogram are excluded from analysis.

Pattern 1 is observed in patients 1, 3, and 7: the first intersinus node electrogram cycle length in a pause is moderately prolonged over the BCL (intersinus node electrogram cycle length less than 150% BCL) and gradually reverts to it, which suggests physiologic overdrive suppression. This is illustrated by figure 7 (patient 3, first postpacing cycle), in which the first intersinus node electrogram cycle length is 940 msec and the last three are about 750 msec (BCL 700 to 820 msec). The progressive shortening of the intersinus node electrogram cycle length from about 1000 msec to 720 msec (BCL 720 to 840 msec) is also clear in figure 6 (patient 1). Figure 4 shows a smaller decrease in intersinus node electrogram cycle length from 1090 to 975 msec (BCL 1000 msec); however, this slight lengthening of the first intersinus node electrogram cycle length in a pause was constant in this patient, with a maximum value of 1200 msec.

Pattern 2 is observed in patients 2, 6, and 8: the intersinus node electrogram cycle length during the pause almost exactly equals the BCL, which suggests the lack of overdrive suppression. This is illustrated by figure 3 (patient 6), in which the first intersinus node electrogram cycle length is 800 msec and the last 750 msec (BCL 700 to 800 msec). In figure 5 (patient 8) the intersinus node electrogram cycle length is 650 msec and the BCL 630 to 680 msec. Figures 2 and 8 (secondary pauses from patient 2) also show intersinus node electrogram cycle lengths of 560 or 580 msec (BCL 600 msec). Triangles in these two figures point to isolated sinus node electrograms without overlapping ventricular repolarization, and circles show slow waves that are strikingly similar to isolated sinus node electrograms. The different relationship of the slow waves from beat to beat to ventricular repolarization suggest that they may be sinus node electrograms. Thus if each of these sinus node electrograms is assumed to be conducted to the next atrial depolarization, there is a first-degree sinoatrial block during basic

**FIGURE 2.** First postpacing cycle and secondary pause in patient 2. From top to bottom: SL (0.5 to 30 Hz), HRA (0.5 to 30 Hz), D, aVF, V, and V. Triangles, isolated sinus node electrograms (S) without overlapping repolarization during pauses; circles, almost equidistant slow waves of similar morphology that may be additional sinus node electrograms as discussed. HRA shows no sinus node electrogram. See also figures 8 and 9 from the same patient. Time marks and abbreviations are as in figure 1.

**FIGURE 3.** First postpacing cycle in patient 6. From top to bottom: SL (0.5 to 30 Hz), HRA (30 to 250 Hz), HRA (0.5 to 30 Hz), D, VF, V. Seven isolated sinus node electrograms (S) are clearly seen in SL and not in HRA (even with higher amplification). Time marks and abbreviations are as in figure 1.
sinus rhythm (sinoatrial conduction time greater than 120 msec). The undisturbed regularity of sinus rhythm with various sinoatrial conduction times is conspicuous in figure 8. Mobitz type I exit block (the first five circles in figure 8) develops along with a shift in atrial depolarization that distinguishes exclusive atrial negativity. This is best exemplified by figure 9, in which a 3/2 Mobitz type I sinoatrial block period explains a secondary pause. Without the advantage of successive isolated sinus node electrograms the basic first-degree sinoatrial block would have been impossible to distinguish from ventricular TU repolarization.

Pattern 3 is illustrated by figure 10 (patient 3, first postpacing cycle) and suggests intrasinus block; a progressive shortening of inter sinus node electrogram cycle length (pattern 1) is followed by an abrupt lengthening (1400 msec) to less than twice the preceding cycle (800 msec, BCL 700 to 820 msec).

**Discussion**

Cramer et al.\(^2\) were the first to provide convincing experimental evidence of a sinus node electrogram. They described a slow diastolic slope corresponding to phase 4 of the sinus nodal action potential and a slow upstroke synchronous with phase 0; the latter was followed by the fast atrial primary negativity. Hariman et al.\(^6\) then extended these findings to humans by first using epicardial electrodes and then the conventional transvenous catheter electrode technique. Previous investigators have used the latter method to compare directly measured and indirectly estimated sinoatrial conduction time.\(^7\,8\,11\,12\)

**Validation of sinus node electrogram in humans.** Validation of these sinus node electrograms in humans, however, remains indirect and relies on occurrence before the P wave and on a similarity to an experimental waveform that has been established only for healthy
FIGURE 6. First postpacing cycle in patient 1. From t1, bottom: HRA (30 to 250 Hz), SL (0.5 to 30 Hz), D1, D2, D3, V1. Four isolated sinus node electrograms (S) are clearly seen in SL; a fifth one may be present after the end of the repolarization of the last paced beat. Time marks and abbreviations are as in figure 1.

sinus nodes with normal sinoatrial conduction. Moreover, this waveform is easily recognized only when the heart rate is slow and a distinct isoelectric plateau separates it from ventricular TU repolarization. We planned to validate sinus node electrograms directly during atrial pauses in patients with sick sinus syndrome and then continue to record the sinus node electrograms after regular cardiac activity resumed in the patients. Castillo Fenoy et al. were the first to take advantage of sinus dysfunction in humans to systematically investigate spontaneous and drug- or stimulation-induced pauses. They attributed each pause in excess of two BCLs to sinoatrial block. Several of their figures showed two successive isolated sinus node electrograms and one figure showed three in a row. The only other example of an isolated sinus node elec-

FIGURE 7. First postpacing cycle in patient 3. From top to bottom: HBE1, HBE2, SL (0.5 to 30 Hz), HRA (30 to 250 Hz), D1, D2, D3, and V1. SL shows baseline drift, a common technical problem at low filter settings. Nonetheless nine isolated sinus node electrograms (S) are apparent during the pause before pacing is resumed. Compare with figures 1 and 10 from the same patient. Time marks and abbreviations are as in Figure 1.
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FIGURE 8. First postpacing cycle and secondary pause in patient 2. From top to bottom: SL (0.5 to 30 Hz), HRA (0.5 to 30 Hz), D1, D3, V1, and V6. As in figures 2 and 9 from the same patient, triangles indicate isolated sinus node electrograms (S) without overlapping repolarization during pauses. Equidistant circles indicate slow waves of similar morphology that may be additional sinus node electrograms as discussed. Assuming conduction of each of these to the following atrial depolarization, the first four-circle sequence suggests Mobitz type I sinoatrial exit block; as in figure 9, prolongation of sinoatrial conduction time is accompanied by a modification of the atrial depolarization (disappearance of the initial negativity), which suggests different exit pathways from the node (catheter motion cannot be excluded). HRA shows no sinus node electrogram. Time marks and abbreviations are as in figure 1.

FIGURE 9. Late secondary pause in patient 2. Disposition, time marks and abbreviations are as in figure 8 (see also figure 2). One isolated sinus node electrogram (S) is shown after a sequence suggesting 3/2 Mobitz type I sinoatrial exit block. Note again the different atrial depolarization (exclusive positivity) after the long sinoatrial conduction time.

trogram can be found in the study of Reiffel et al.8 We prospectively studied eight patients with sick sinus syndrome who had very long pauses so that repetitive localized low-frequency deflections could be clearly identified in the absence of any overlapping activity. Positive pauses were consistently recorded in six of these patients. We believe that this pattern validates sinus node electrograms. This belief is reinforced by the fact that intersinus node electrogram cycle length approximates BCL and that continuous electrical activity is demonstrated by a slow diastolic slope bridging sinus node electrogram intervals. The consistent recording of continuous electrical activity with a slow diastolic slope is evidence against the possibility that nonautomatic perinodal atrial tissue, insulated from the outer atrium and fired by the sinus node, may be responsible for the local electrograms.

Limitations of the study. Although we demonstrated automatic electrical activity with a cycle length approximating the BCL, localized to the expected site of the sinus node, and unexplained by any known artifact, we have not proved that this activity is actually driving
the atrium during basic sinus rhythm. Therefore existence of sinoatrial block is debatable. Conceivably, we may have recorded local automatic activity originating in sinus remnants or abnormal atrial cells insulated from the atrium (exit block), thus having no physiologic significance. In this case the unrecorded pacemaker may have been suppressed by rapid atrial pacing and these sinus dead ends (coupled to the pacemaker but protected from overdrive suppression by entrance block) may have escaped. However, the following points have to be considered.

First, the amplitude of recorded sinus node electrograms, which is best evaluated by comparison with the amplitude of the local atrial electrogram (19%, range 10% to 30%), indicates that a significant mass of synchronized cells is involved.

Second, the similarity of intersinus node electrogram cycle length and BCL suggests the presence of a common pacemaker.

Third, obviously the problem of conduction is addressed more directly in settings opposite to those selected for this study, i.e., during sinus pacemaker conduction to the atrium. In this regard, a basic first-degree sinoatrial block by direct recording was suggested in patient 2, while patients 6 and 7 showed a dominant pacemaker pattern during regular sinus rhythm. Moreover, each time the cycle length was observed to increase after an extrasystole, the sinus node electrogram in its precise waveform was seen to partially or totally emerge from the atrial fast complex in an accordion-like pattern (patients 7 and 8). Thus, except for patients 1 and 3 (low amplification, no extrasystole), a consistent temporal relationship was observed between sinus node electrogram and atrial depolarization during sinus rhythm. Although conduction is only inferred from this temporal relationship, this limitation is common to all studies short of microelectrode mapping. 13, 14

Mechanism of the pauses. Postpacing pauses are thought to result from overdrive suppression. 15 This view is based on experimental data on both normal and chemically or physically altered sinus nodes. 16, 17 The mechanisms of overdrive suppression are not clear. Local acetylcholine release is an accessory factor and depression of the rate of phase 4 spontaneous depolarization is deemed essential. Initial studies implicated sinus hyperpolarization, 16 while more recent studies demonstrated sinus depolarization 17 during the very long postpacing pauses induced by cold or by digitalis toxicity. Finally, intrasinus block with subthreshold oscillations that eventually arrest may be another contributory mechanism of overdrive suppression. 16

Our results challenge these views and strongly suggest that sinoatrial block is the major mechanism of abnormally prolonged postpacing atrial pauses in patients with sick sinus syndrome. Spontaneous and postspacing 2:1 sinoatrial block by conventional ECG criteria in patient 3 (figure 1, tracing B) and 6 supports this mechanism as the reason for the longer pauses. In patients with positive pauses, the lack of any overdrive

FIGURE 10. First postspacing cycle in patient 3 (see also figures 1 and 7). From top to bottom: HBE1, HBE2, SL (0.5 to 30 Hz), HRA (30 to 250 Hz), D1, D2, D3, and V1. Five sinus node electrograms (S) are shown during the pause. The progressive shortening of the intersinus node electrogram cycle length (pattern 1) is followed by an abrupt lengthening (1400 msec) to less than twice the preceding cycle (800 msec; BCL 700 to 820 msec), which suggests intrasinus block. This pattern was seen only in this patient and on two occasions. Time marks and abbreviations are as in figure 1.
suppression (pattern 2) or the presence of only physiologic overdrive suppression (pattern 1) without any escape interval exceeding 150% BCL after the end of the last ventricular repolarization, suggests that diseased nodes are not subject to the kind of major overdrive suppression experimentally observed with cold or with digitalis toxicity and/or that high-grade atrio-sinus entrance block develops during rapid atrial pacing.\textsuperscript{18, 19} Due to overlap with the TU repolarization of the last paced beat, no short escape interval suggesting entrance block (less than one intersinus node electrogram cycle length) could be identified except in patient 2 (compare figures 2 and 8; note the first circle of the recording in figure 2 and the first postspacing cycle in figure 8).

The mechanism and sites of this postspacing exit block are not known. This is unlike the activity of TTX, which specifically exerts its effects on fast-channel atrial tissue. The similarity of conducted and non-conducted sinus node electrograms favors a modification of the perinodal tissue (or atrial sink, transition from slow to fast channels) rather than of the source as the cause for the exit block.

Marked fibrosis of the approaches to the sinus node consistently observed in one anatomic study\textsuperscript{20} of patients with sick sinus syndrome may offer a morphologic basis for the low safety factor of conduction. Although Bharati et al.\textsuperscript{21} reported two cases of essentially normal nodes with fibrotic approaches in adolescents with sick sinus syndrome, the sinus node is more often markedly fibrotic.\textsuperscript{20, 22}

Therefore we conclude that (1) sinus node electrogram recording is possible but baseline drift is the major problem, (2) it is of value in understanding atrial pauses, (3) long postspacing pauses are generally (in six out of eight patients) caused by sinoatrial block, (4) the mechanism of this sinoatrial block is not known, and (5) different patterns of sinus node electrograms are observed during pauses, thus making indirect interpretation unreliable.

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