Analysis of Secondary Pauses Following Termination of Rapid Atrial Pacing in Man

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SUMMARY The first ten cycles following cessation of atrial pacing were evaluated in 44 control subjects (mean age 52.9 ± 14.88 yr) and 39 patients (mean age 62.9 ± 15.41 yr) suspected of having sinus node dysfunction (SND). The maximal cycle length for each post-pacing cycle following several pacing periods in each control subject was determined, and was normalized by dividing it by the subject’s mean spontaneous control cycle length (SCL). Using the control group, a normalized maximal post-pacing response pattern (mean and SD) was derived. For each SND patient, a composite SD for each post-pacing cycle was calculated by adding the patient's SCL variance to the variance determined for each post-pacing cycle in the control group. Two composite SD above the mean value for each post-pacing cycle was selected as the upper limit of the normal recovery response and used to identify abnormal post-pacing responses in the 39 SND patients. Abnormally prolonged cycle lengths subsequent to the first escape cycle (secondary pauses) were found in 16/39 (41.0%) patients, of whom 11/39 (28.2%) had a prolonged SNRTmax. Of importance, 11/12 (91.7%) patients with documented SA block or sinus pauses prior to electrophysiologic study, demonstrated secondary pauses, while only 7/12 (58.3%) had a prolonged SNRTmax. Criteria are derived for the identification of secondary pauses during the post-pacing period, and a close association between secondary pauses and the presence of spontaneous SA block or sinus pauses prior to electrophysiologic study is demonstrated.

THE DEGREE OF PROLONGATION of the first escape cycle following termination of rapid atrial pacing has been proposed as a means of characterizing disturbances of automaticity in patients with sinus node dysfunction.1-7 However, recent studies of patients with sinus node dysfunction have noted abrupt prolongations of cycle lengths subsequent to the first post-pacing cycle.8-11 The significance of these recent findings is unknown but suggests that the presence of abnormalities in cycles subsequent to the first post-pacing cycle may be useful in evaluating patients with sinus node dysfunction.

The object of this study was to examine the first ten post-pacing cycles in a group of normal patients and in a group of patients suspected of having sinus node dysfunction. Criteria are established for the diagnosis of abnormally prolonged cycle lengths in the early post-pacing period, and the frequency and significance of these abnormalities are evaluated.

Methods

Thirty-nine patients (mean age 62.9 ± 15.41 yr) with clinical features suggestive of sinus node dysfunction were studied. Documented electrocardiographic (ECG) manifestations included sinus bradycardia (31 patients), sinoatrial (SA) block (8 patients), sinus pauses (5 patients) or bradycardia-tachycardia syndrome (7 patients).12-14 Symptoms included syncope, dizziness, palpitations, chest pain and dyspnea.

A control group of 44 patients (mean age 52.9 ± 14.88 yr) was also studied. The control patients had no clinical or electrocardiographic evidence of sinus node disease, but were referred because of chest pain. They were studied either during the course of diagnostic cardiac catheterization (prior to the injection of contrast material), or during atrial pacing studies for evaluation of chest pain. Patients who were considered to have significant coronary artery disease, i.e., greater than 50% stenosis of a major coronary artery, or who developed chest pain or ECG manifestations of myocardial ischemia during atrial pacing were excluded from the control group.

Prior to study a complete history, physical examination, chest X-ray, ECG and signed informed consent were obtained on all patients. At the time of study all cardioactive medications had been discontinued for an interval exceeding three drug half-lives.

All of the patients were studied in a catheterization laboratory in the resting, nonsedated, postabsorptive state. A quadripolar electrode catheter was inserted via a peripheral vein and positioned against the high lateral right atrial wall. The cephalic electrode pair was used for atrial stimulation and the high right atrial electrogram was recorded from the caudal pair. The atrium was stimulated with a 2 msec constant current pulse at approximately two times atrial diastolic threshold.

The atrial electrogram and two or more limb leads of the ECG were simultaneously displayed on an oscilloscope and recorded on FM magnetic tape. The records for analysis were subsequently obtained by playback to an Elema Mingograf 800 recorder at a paper speed of 100 mm/sec or were recorded directly on photographic paper at a paper speed of 100 mm/sec using an Electronics for Medicine recorder.

Following a 15-20 min stabilization period, control recordings were obtained in each patient. The right atrium was then paced for 60 second periods, at constant cycle lengths of 860, 660, 540, 460, 400 and 353 msec (70, 91, 111, 130, 150, 170 beats/min). Occasionally intermediate cycle lengths (e.g.: 1000, 760, 600 and 500 msec or 60, 79, 100 and 120 beats/min) were also used, and frequently more than one pacing run was done at each cycle length. During the pacing periods the rhythm was carefully monitored to ensure complete atrial capture. At least 45 seconds elapsed between pacing periods, during which time the rhythm was monitored to assure a return to control cycle length before the next pacing period was started.
Records obtained from all patients were analyzed in the following manner. Twenty consecutive cycles in the control recordings were used to calculate the mean prepacing spontaneous cycle length (SCL). Following each pacing period the duration of each of the first ten cycles was measured. The interval between the last paced atrial depolarization and the first spontaneous atrial depolarization defined the first cycle and subsequent cycles were sequentially numbered. Each cycle was normalized by dividing its duration by SCL. The longest first post-pacing cycle or maximum sinus node recovery time (SNRTmax) was determined for each patient. Each post-pacing record was carefully examined for the presence of sinus P waves. If atrial premature depolarizations or junctional escape beats with atrial capture (2 patients) were present, the cycles preceding and following the ectopic beat were excluded from further analysis.

In each control patient, several pacing cycle lengths were tested and the longest normalized cycle length of each of the first ten post-pacing cycles was determined. The mean maximum normalized cycle length, standard deviation and variance (sd²) for the control group were calculated for each post-pacing cycle (table 1) and hereafter will be referred to as the control group mean cycle lengths, the control group standard deviations and the control group variances, respectively. The control group was subdivided into two subgroups, A and B. Group A consisted of 21 patients whose SCL > 800 msec, and group B consisted of 23 patients whose SCL < 800 msec. Fifty-eight pacing studies were performed in group A patients and 72 pacing studies were performed in group B patients. The mean maximum normalized cycle length and two standard deviations for each post-pacing cycle defines a normalized maximal recovery response for each subgroup (table 1). Figure 1 illustrates such a recovery response for Group A.

Records obtained from the 39 patients suspected of having sinus node dysfunction were analyzed in the following manner. The standard deviation and variance of SCL were determined for each patient and the post-pacing response was compared with the control subgroup (group A or group B) which encompassed the patient’s SCL. The variance of SCL in each patient as well as the appropriate control subgroup variance for each post-pacing cycle were used to calculate a composite normalized standard deviation for each post-pacing cycle by taking the square root of the summed variances. A cycle length was defined as abnormally prolonged if it was greater than two composite standard deviations above the mean value established for that post-pacing cycle. An abnormal prolongation of any cycle subsequent to the first post-pacing cycle was referred to as a secondary pause. Secondary pauses may be detected in cycles terminated by atrial or junctional escape beats, as well as in cycles considered to be of sinus node origin. In the former cases, the cycle length of the escape beat is considered to be less than the cycle length of the anticipated atrial depolarization of sinus node origin.

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\begin{array}{cccccccccc}
\text{Control group (N = 44)} & & & & & & & & & \\
\text{Mean} & 1.35 & 1.22 & 1.14 & 1.08 & 1.07 & 1.05 & 1.03 & 1.03 & 1.05 & 1.07 \\
\text{sd} & .202 & .201 & .202 & .118 & .115 & .099 & .114 & .102 & .088 & .084 \\
\text{Variance} & .041 & .040 & .041 & .014 & .013 & .010 & .013 & .010 & .008 & .007 \\
\text{Mean + 2 sd} & 1.75 & 1.62 & 1.54 & 1.32 & 1.30 & 1.25 & 1.26 & 1.23 & 1.23 & 1.24 \\
\end{array}
\]

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\begin{array}{cccccccccc}
\text{Control group A} & & & & & & & & & \\
\text{(SCL > 800 msec) (N = 21)} & & & & & & & & & \\
\text{Mean} & 1.26 & 1.18 & 1.11 & 1.07 & 1.05 & 1.03 & 0.96 & 0.99 & 1.02 & 1.00 \\
\text{sd} & .174 & .192 & .190 & .133 & .106 & .088 & .100 & .079 & .083 & .052 \\
\text{Variance} & .030 & .037 & .036 & .018 & .011 & .008 & .010 & .006 & .007 & .003 \\
\text{Mean + 2 sd} & 1.61 & 1.56 & 1.49 & 1.34 & 1.26 & 1.21 & 1.16 & 1.15 & 1.19 & 1.10 \\
\end{array}
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\begin{array}{cccccccccc}
\text{Control group B} & & & & & & & & & \\
\text{(SCL < 800 msec) (N = 23)} & & & & & & & & & \\
\text{Mean} & 1.44 & 1.26 & 1.18 & 1.09 & 1.10 & 1.08 & 1.07 & 1.06 & 1.07 & 1.10 \\
\text{sd} & .193 & .204 & .210 & .104 & .120 & .105 & .103 & .113 & .095 & .085 \\
\text{Variance} & .037 & .042 & .044 & .011 & .014 & .011 & .011 & .013 & .009 & .007 \\
\text{Mean + 2 sd} & 1.83 & 1.67 & 1.60 & 1.30 & 1.25 & 1.29 & 1.28 & 1.29 & 1.26 & 1.27 \\
\end{array}
\]

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\begin{array}{cccccccccc}
\text{Post-pacing cycle} & & & & & & & & & \\
\text{1} & 2 & 3 & 4 & & & & & & \\
\end{array}
\]

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\begin{array}{cccccccccc}
\text{Figure 1. The limits of the normal recovery response for control group A (SCL > 800 msec) are determined by the normalized maximum mean cycle lengths + 2 sd for each of the first ten post-pacing cycles. In every control patient in group A the maximum value for each post-pacing cycle was obtained from data accumulated following several pacing runs. The maximum value of each cycle length was normalized by dividing it by SCL in each control patient, and the group mean value and sd were then derived for each cycle. The normalized mean value (1.0) and the 2 sd bars for the variation of cycle length exhibited by this group of patients during the prepacing control period are shown to the left of the vertical bar.}
\end{array}
\]
Post-pacing Responses in Control Patients

1) **Interpatient variability** of response to rapid atrial pacing was evaluated in a control group of 44 patients (SCL 782 ± 132.5 msec). One-hundred and thirty pacing studies were performed in these 44 patients.

For the control group as a whole the mean value for the normalized SNRT_max (msec) was (1.35 ± 0.202) SCL. Linear regression analysis of the relationship between SNRT_max and SCL (msec) identified the best fit straight line to be equal to 0.95 × SCL + 310 msec (r = 0.65).

The mean normalized recovery responses for group A (mean SCL 890 ± 80.5 msec) and group B (mean SCL 684 ± 84.1 msec) are shown in table 1, and demonstrate similar recovery patterns. Control group mean cycle lengths show a progressive decline approaching control values by the fourth post-pacing cycle.

2) **Intrapatient variability** of cycle length, determined in the control period prior to pacing, must be considered in the evaluation of post-pacing cycles. For the majority of the patients (34/39) SCL variance was small relative to the control subgroup variance resulting in negligible differences between the composite recovery response for each of these patients and the control subgroup recovery response. Important discrepancies between composite and control subgroup recovery responses were, however, noted in five patients with marked sinus arrhythmia.

Figure 2 illustrates the derivation of the composite envelope of the post-pacing response curve in a patient who exhibited marked sinus arrhythmia (SCL 934 ± 186 msec, mean ± 1sd) during the control period. Since this patient's SCL exceeded 800 msec, the control data from group A are employed. The light interrupted lines in figure 2 indicate the group A response pattern (identical to fig. 1). The solid lines indicate the calculated composite 2 so limit for each post-pacing cycle. A typical post-pacing response obtained from this patient is shown by the dark interrupted line. It is evident that there are marked fluctuations of cycle lengths in the post-pacing period which may be a result of sinus arrhythmia in this patient, but which would have been interpreted as abnormal (particularly cycle 5) if the composite response envelope had not been derived.

**Post-pacing Response In Patient With Suspected Sinus Node Dysfunction**

Post-pacing responses in each of the 39 patients (group mean SCL 1033 ± 241.7 msec) were studied. In 33/39 SCL exceeded 800 msec and the post-pacing responses were compared with control group A. In the remainder of the patients (6/39) SCL was less than 800 msec and the post-pacing responses were compared with control group B.

The SNRT_max was prolonged (greater than the sum of the mean maximum cycle length + 2 composite standard deviations) in 11 of 39 (28.2%) patients. Secondary pauses, defined as abnormal prolongation of any of cycles 2 through 10 (greater than the sum of the appropriate control group mean cycle length + 2 composite standard deviations), were present in 16 of 39 (41.0%) patients. Any of cycles 1 through 10 was prolonged in 18/39 (46.2%) patients (table 2).

In general, abnormalities of cycles subsequent to the first post-pacing cycle tended to occur more frequently at the more rapid pacing rates. For example, 32/41 (78%) post-pacing periods with secondary pauses appeared at pacing cycle lengths less than 660 msec (greater than 91 beats/min).

Analysis of the post-pacing responses in the 16 patients with suspected sinus node dysfunction who demonstrated abnormalities in cycles 2–10, revealed two basic patterns. A Type I response (fig. 3, left and middle panels) consisted of an abrupt increase in the duration of one or more cycles during the post-pacing period. In 9/16 (56.3%) patients the increase in cycle length was close to a whole number multiple of the mean value predicted for that cycle by the normal
Table 2. Post-pacing Cycle Abnormalities

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Frequency of abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patient group (N = 39)</td>
<td></td>
</tr>
<tr>
<td>Patients with documented SA block or sinus</td>
<td>13/39 (33.3%)</td>
</tr>
<tr>
<td>cycles (N = 12)</td>
<td></td>
</tr>
<tr>
<td>Control group A (SCL &gt; 800 msec) (N = 21)</td>
<td>8/12 (66.7%)</td>
</tr>
<tr>
<td>Control group B (SCL &lt; 800 msec) (N = 23)</td>
<td>1/23 (4.3%)</td>
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</tbody>
</table>

*Maximum corrected sinus node recovery time (CSRT = SNRTmax - SCL) exceeding 525 msec.
†SNRTmax (maximum sinus node recovery time) exceeding 1680 msec.
‡Post-pacing cycle lengths exceeding the predicted mean value for that cycle + 2 composite SD.

response curve (fig. 3 left). In 13/16 (81.3%) patients the cycle length was prolonged, but less than a whole number multiple of the predicted mean value for that cycle (fig. 3 middle). In some instances, in contrast to the abrupt change in cycle length, characteristic of the Type I response, the abnormally long post-pacing cycles gradually decreased toward normal values. A delayed recovery pattern of this type, which is illustrated in figure 3 right, is called a Type II response and occurred in 5/16 (31.3%) patients.

Twelve of 39 patients had electrocardiographic evidence (routine ECG and/or ambulatory ECG monitoring) of SA block or sinus pauses prior to electrophysiologic study. These manifestations were infrequent and episodic, and in addition, analysis of 100 cycles during the control period of the electrophysiologic study in each patient showed that only one of the 12 patients had episodes of spontaneous SA block or sinus pauses prior to pacing (frequency of occurrence 9/100 cycles). In contrast to the findings of the control period, 11/12 (91.7%) patients had abnormal prolongations of cycles subsequent to the first post-pacing cycle.

Twenty of the 39 patients with suspected sinus node dysfunction had sinus bradycardia as the sole electrocardiographic finding. Only three of 20 (15%) patients demonstrated abnormalities in post-pacing cycles 2–10, and only 4/20 (20%) patients had a prolonged SNRTmax. In addition, 4/7 (57.1%) patients with the bradycardia-tachycardia syndrome showed abnormalities in post-pacing cycles 2–10 and only 2/7 (28.6%) patients had a prolonged SNRTmax. There was no correlation between these electrocardiographic abnormalities and the type of abnormal response pattern seen in the post-pacing period.

Discussion

Although previous studies have described prolongations of post-pacing cycles in patients suspected of having sinus node dysfunction, the clinical significance of this finding has not been evaluated.8–11 In this report we describe criteria for the identification of secondary pauses during the post-pacing period and demonstrate a close association between the incidence of spontaneous SA block and/or sinus pauses prior to electrophysiologic study and secondary pauses elicited during electrophysiologic study.

Criteria for the normal post-pacing period must take into account both the variability in responses to pacing in a group of normal patients, as well as the variability in spontaneous cycle length within an individual patient. Based on the con-

Figure 3. Typical post-pacing responses illustrating the patterns of secondary pauses are shown for three different patients. The solid lines indicate the composite 2 SD limits for each post-pacing cycle for the patient whose response is depicted. The empty circles connected by the heavily hatched lines indicate a typical post-pacing response in the three patients. In these cases, each patient had SCL > 800 msec and the standard deviations about the mean maximum cycle lengths are derived from group A. The normalized SCL ± 2 SD for each patient is shown to the left of the vertical bar in each panel. The left-hand panel illustrates a Type I response in which there is an abrupt increase in cycle length to a value close to twice the predicted value for that cycle. The middle panel depicts a Type I response in which the prolongation does not approach a whole number multiple of the predicted value for that cycle. The right-hand panel illustrates a delayed recovery or Type II response. Note that the SNRT is normal in this case.
control group data (normalized by SCL), the mean values of maximal cycle length for the normal post-pacing recovery period were established. Using the control subgroup mean variance and the variance of the spontaneous cycle length in an individual patient, a composite standard deviation was calculated. Two composite standard deviations above the mean value for each post-pacing cycle was selected as the upper limit of the normal recovery response in order to minimize the possibility of identifying a prolonged post-pacing cycle as a secondary pause when it may have been due to random spontaneous variation in cycle length.

Previous studies have emphasized the value of SNRT measurement in the evaluation of sinus node function. Abnormal prolongation of the first post-pacing cycle would have been diagnosed in 13/39 (33.3%) patients using the previously published criteria of either Narula et al. or Dhingra et al., and was diagnosed in 11/39 (28.2%) patients by our criteria (table 2). Interestingly, 7/11 (63.6%) patients with a prolonged SNRTmax, using our criteria, had documented episodes of sinus pauses and/or SA block. Secondary pauses, identified in 16/39 (41.0%) patients, were more commonly observed than were abnormalities of SNRTmax. Of particular interest is the fact that 11 of 16 patients (68.8%) with secondary pauses had prior documentation of SA block or sinus pauses. In fact, of 12 patients with SA block or sinus pauses documented prior to electrophysiologic study, 11 (91.7%) demonstrated secondary pauses after termination of atrial pacing. In these 12 patients, the frequent occurrence of secondary pauses during the post-pacing period cannot reasonably be attributed to chance occurrence of SA block or sinus pauses, as only one patient demonstrated these abnormalities during the prepping control period. It is of further interest that while secondary pauses occurred in 11/12 patients, abnormalities of the first post-pacing cycle were present in only 7/12 (58.3%) patients (table 2). Although these differences are not statistically significant, they suggest that secondary pauses may be a more sensitive indicator of the presence of spontaneous SA block or sinus pauses in patients than are first cycle abnormalities. On the other hand, it should be recognized that the specificity and sensitivity of the pacing technique in the evaluation of patients for SA block and sinus pauses can only properly be evaluated in a prospective study.

Secondary pauses appear to fall into two patterns. Although there was no significant correlation between the type of secondary pause and the pre-existing electrocardiographic manifestations, these patterns may be helpful in speculating on the underlying electrophysiologic mechanisms. A Type I secondary pause was defined as an abrupt prolongation of cycle lengths subsequent to the first escape cycle. A prolongation which was close to a whole number multiple of the predicted value for that cycle favors the occurrence of SA exit block as the underlying mechanism, and was seen in 9/16 (56.3%) patients. The site of block could be either within the sinus node or between the sinus node and atrium, or could also represent subthreshold oscillations that fail to reach threshold potential. A prolongation of cycle length which was less than a whole number multiple of the predicted value for that cycle was the most frequent finding, occurring in 13/16 (81.3%) patients. This type of abnormality could result from a disturbance of conduction or a disturbance of automaticity, either of which could produce a shift in pacemaker site. A Type II response pattern consisted of a sustained prolongation of the post-pacing cycles for more than three cycles following termination of pacing. A delayed recovery pattern of this type was the least frequent finding, occurring in 5/16 (31.3%) patients. Although this disturbance suggests a depression of automaticity, conceivably a depression of conduction or subthreshold oscillations could also produce these findings.

The sinus node is richly innervated, and any of the electrophysiologic mechanisms previously discussed may result from increased concentration of acetylcholine at the receptor sites or from increased tissue sensitivity to the effects of physiologic concentrations of acetylcholine. It has been suggested that acetylcholine may be released during the period of pacing as well as during the post-pacing period. The released acetylcholine could prolong sinoatrial conduction by decreasing membrane resistance, decreasing the upstroke velocity of the transmembrane potentials recorded from cells of the sinoatrial node (unpublished observations) or could depress automaticity by hyperpolarizing the membrane and decreasing the slope of phase 4 depolarization of the sinus node transmembrane potentials.

Prolonged pauses following termination of paroxysmal atrial tachycardia have been noted previously. Furthermore, prolongation of post-paroxysmal cycles, analogous to the secondary pauses following termination of atrial pacing, have been illustrated previously. There may be an analogy between the prolonged post-paroxysmal pause and the prolonged SNRTmax. If this were the case, then prolonged post-paroxysmal pauses would indicate sinus node dysfunction. However, interventions used to terminate paroxysmal atrial tachycardia may cause an increase in the concentration of liberated acetylcholine within the sinus node. As a result, the post-paroxysmal pause may be prolonged in the absence of sinus node dysfunction.

In summary, we have described a method for the identification of secondary pauses following atrial pacing based on the development of a predicted mean value and composite standard deviation for each post-pacing cycle. This approach may be simplified in patients who do not exhibit marked variation in cycle length during the control period. In these cases the composite standard deviation does not differ appreciably from the control group standard deviation and the values listed in table 1 may be used directly to determine post-pacing abnormalities in an individual patient.

We have also shown that secondary pauses during the post-pacing period occur frequently in patients with spontaneous SA block or sinus pauses diagnosed prior to electrophysiologic study. These secondary pauses may occur at times when the SNRTmax is normal. Our data suggest that the identification of secondary pauses increases the value of the atrial pacing technique as a provocative test for the evaluation of patients suspected of having sinus node dysfunction.

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