Acceleration of Sinus Rhythm During Slow-rate Atrial Pacing

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SUMMARY We evaluated the effects of slow-rate atrial pacing on impulse formation of the sinus node in 13 isolated rabbit right atria using the microelectrode technique. After the spread of activation was mapped to determine true sinoatrial conduction time (SACT) (38 ± 16 msec [± sd]), the atrium was paced for eight beats at constant intervals slightly shorter than spontaneous cycle length in steps of 10 msec. In all preparations, slow-rate atrial pacing failed to capture the pacemaker center, but shortened action potential duration because of electrotonic interaction between atrium and sinus node. The resulting acceleration of impulse formation of dominant fibers ceased instantaneously when atrial pacing was terminated.

Estimation of SACT by constant pacing 5 beats/min faster than sinus rhythm seriously underestimated the true values (p < 0.05), because sinus node acceleration prevented capture of dominant pacemaker fibers in 10 of 13 preparations. At pacing rates 10 beats/min faster than sinus rhythm, capture did not occur in eight of 13 experiments; at pacing rates 20 beats/min faster, the pacemaker center was captured in all preparations.

This study describes sinus node acceleration as a consistent and hitherto unknown finding during slow-rate stimulation of the atrium. This phenomenon accounts for the failure of the constant atrial pacing technique to determine SACT accurately in man.

IN 1973, Strauss and co-workers proposed premature atrial stimulation as an indirect measure of sinoatrial conduction time (SACT) in man.1 Subsequent experimental studies have shown several inherent inadequacies of this technique.2,3 Using constant atrial pacing at rates slightly faster than sinus rhythm, Narula et al.4 found a simpler and quicker approach for measuring SACT. Data obtained by constant atrial pacing have been used to characterize sinus node function in man5-7 and also have been compared for validation with the results of independent method of direct extracellular direct-current recordings of sinus node activity.8

Testing the Narula technique in an experimental microelectrode study, we consistently found an acceleration of sinus node automaticity during slow-rate atrial drive. In this report, we describe the electrophysiologic mechanism of this acceleration and the resulting pitfalls when SACT calculation is performed by this technique.

Methods

Young rabbits that weighed 1.5–2.5 kg were killed by a blow on the neck. The hearts were rapidly excised and dissected in cool Tyrode’s solution. The right atrium was isolated from the remaining part of the heart and pinned with its endocardial surface uppermost in a tissue bath, which was perfused with oxygenated Tyrode’s solution at 50 ml/min.

The composition of the modified Tyrode’s solution was (in mM): NaCl, 130; KCl, 4.7; CaCl2, 2.5; MgCl2, 2.6; NaHCO3, 24.9; NaH2PO4, 1.3; glucose, 11. The solution was bubbled with 98% O2 and 2% CO2 to achieve a pH of 7.35 ± 0.05 and temperature was maintained at 37 ± 0.1°C.

A pair of Teflon-coated silver wires was placed on the midportion of crista terminalis to record a bipolar electrogram; a second pair of electrodes was positioned on the atrial appendage to stimulate the preparation. A programmable stimulator (Arrhythmia Investigation System Type 4279, Digitimer LTD) provided single stimuli with variable prematurity after every tenth spontaneous beat of sinus origin or a train of stimuli with variable pacing intervals and duration of pacing. Stimuli were constant 2-msec voltage pulses, twice threshold.

Transmembrane potentials were recorded with glass microelectrodes filled with 3M KCl (resistance 10–20 MΩ). All signals were displayed on a storage oscilloscope (Tektronix 5103N), stored on magnetic tape (Ampeex PR 2200, tape speed 15 inches/sec) and recorded on a Minograf 804 (Siemens) for detailed analysis.

All preparations beat spontaneously.

The pacemaker site was identified by extensive mapping of the endocardial sinus node area using 40–60 intracellular impalements as previously described.3 Dominant pacemaker fibers exhibit marked phase 4 depolarization, a smooth transition between phase 4 and phase 0 of the action potential, and the longest latency between activity of the cell and the atrium.

After a stable impalement of a dominant pacemaker fiber had been achieved, the preparation was paced for a train, started at random, or eight beats at a constant interval 10 msec shorter than spontaneous cycle length. This pacing run was performed four times, interposed with intervals of 20 spontaneous cycles. Then, the pacing interval was shortened further in steps of 10 msec. These steps equalled a change of pacing rate of 2.3–4.7 beats/min.

Data Analysis

SACT was defined as the time between the activation of a dominant pacemaker fiber and atrial activa-
tion. We defined the moment of activation as the 50% amplitude of the transmembrane potential of a fiber during phase 0 depolarization and the intrinsic deflection of the surface electrogram.

The action potential duration was measured from the moment of activation of a fiber to the time at which repolarization was 90% complete. In each preparation, we determined the slowest pacing rate that led to a sharp transition between phase 4 and phase 0 depolarization of the dominant sinus node fiber; this we defined as sinus node capture.

Sinus node recovery time (SNRT) after a train of constant atrial pacing was measured as the interval between the last paced atrial electrogram and the first spontaneous atrial electrogram of sinus origin.

To compare data from several experiments with different basic cycle lengths, we calculated the corrected recovery time (CSNRT) as sinus node recovery time minus spontaneous cycle length before stimulation. Corrected recovery time of dominant pacemaker fibers was measured from phase 0 depolarization after the last paced atrial beat to phase 0 depolarization of the first spontaneous sinus node action potential.

For estimation of SACT by constant atrial pacing, the atrial return cycle after a train of eight consecutive stimuli was measured and divided by two (undirectional SACT). For calculation of SACT by premature atrial stimulation, the postextrasystolic cycles of the atrium A1A2 were plotted as a function of the curtailed cycle A1A2. SACT transition was calculated from A1A2 at transition from compensatory to noncompensatory return cycles and SACT50% from A2A3 after a curtailed cycle that was 50% of spontaneous cycle length.

Statistical evaluation was by linear regression analysis and Wilcoxon matched-pairs, signed-rank tests.

Results

Acceleration of Sinus Rate

In 13 experiments, various pacing rates slightly faster than sinus rhythm were applied with a microelectrode impaled in a dominant pacemaker fiber. Figure 1 depicts a representative experiment.

Panel A shows the transmembrane potential of a pacemaker fiber (upper trace) and the surface electrogram of crista terminalis (lower trace) during spontaneous rhythm. The spontaneous cycle length is 455 msec and the true SACT is 58 msec. Although the preparation was paced at an interval of 440 msec (panel B), activation of the fiber still precedes the activation of the atrium by 10 msec, and phase 4 depolarization merges smoothly into phase 0 depolarization. Thus, the atrial impulses do not capture the pacemaker fiber. Nevertheless, sinus node impulse formation is accelerated due to a shortening of action potential duration from 194 msec to 176 msec.

In panel C, the pacing interval is 410 msec. The transition from phase 4 to phase 0 depolarization is more marked, but still gradual, indicating that the fiber continues to discharge spontaneously. The action potential duration is shortened to 154 msec, which leads to a further decrease of sinus node cycle length. The atrial deflection precedes activation of the pacemaker fiber by 32 msec, but the impulses fail to capture the pacemaker center. At a pacing interval of 380 msec (panel D), a sharp transition from phase 4 to phase 0 depolarization occurs, indicating that the fiber is prematurely discharged by the paced atrial beats. Atrial conduction time is 44 msec. Thus, sinus node capture in this preparation does not occur until the pacing interval is 75 msec shorter than spontaneous cycle length.

In figure 2, the transmembrane potential of a dominant pacemaker fiber during spontaneous rhythm at a cycle length of 455 msec (broken) and during atrial pacing with an interval of 410 msec (solid) is superimposed. During stimulation, phase 4 depolarization of the fiber continues to merge gradually into action potential upstroke. Nevertheless, the transmembrane potential is influenced by the atrial impulses. Phase 0 depolarization and repolarization are speeded up; as a consequence, the duration of the action potential is shortened.

In all 13 experiments, the atrial stimuli failed to capture the dominant pacemaker fibers when the pacing cycle closely approached the spontaneous cycle length. During noncapture, the action potential dura-
tion of pacemaker fiber was shortened, the maximal degree of shortening varying from preparation to preparation. Prolongation of the stimulation period in eight experiments up to 60 seconds did not alter the phenomenon of sinus node acceleration.

Table 1 lists complete data from 13 experiments. Preparations 1–7 exhibited a long SACT (> 30 msec) and preparations 8–13 exhibited a short SACT (≤ 30 msec) during spontaneous rhythm. The length of true SACT is positively correlated to action potential duration of dominant pacemaker fibers ($r = 0.854, p < 0.01$). Also, the pacing rate necessary to capture the pacemaker center is positively correlated to action potential duration ($r = 0.859, p < 0.01$) and true SACT ($r = 0.843, p < 0.01$). Thus, the longer the action potential duration during spontaneous rhythm, the more pronounced the shortening of action potential duration and the extent of sinus node acceleration during atrial pacing. In preparations with a long SACT (nos. 1–7), capture of dominant pacemaker fibers occurred only at pacing rates at least 14 ± 3 beats/min faster than spontaneous rhythm (range 12–20 beats/min). In preparations with a rather short SACT (nos. 8–13), capture occurred at pacing rates 6 ± 3 beats/min faster than sinus rhythm (range 2–9 beats/min) (table 1).

Sinus node acceleration during atrial pacing developed independent of the prematurity of the first paced beat, as long as the spontaneous cycle and the pacing cycle differed enough to influence the sinus node at all.

**Determination of SACT**

In 13 experiments, we compared true SACT, determined by intracellular “mapping,” and estimated SACT, determined by premature atrial stimulation and constant atrial pacing (table 1). Premature atrial stimulation underestimates true SACT when estimation is based on an atrial return cycle at transition from compensatory to noncompensatory pause (transition methods).\(^2\)\(^3\) Estimated SACT derived from the length of $A_A$, after a curtailed cycle of 50% of $A_A$, tends to overestimate true values. For constant atrial pacing,

**TABLE 1. Electrophysiologic Data from 13 Experiments**

<table>
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<tr>
<th>Experiment</th>
<th>Cycle length (msec)</th>
<th>SACT (msec)</th>
<th>APD (msec)</th>
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<th>Constant pacing</th>
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| Mean ± sd | 444 ± 52 | 38 ± 16 | 153 ± 30 | 20 ± 11 | 40 ± 13 | 22 ± 8* |

*p < 0.05 vs true SACT.

Abbreviations: SACT = sinoatrial conduction time; APD = action potential duration.
estimation of SACT depends on atrial pacing rate.

At stimulation rates only 5 beats/min faster than sinus rhythm, true SACT was underestimated in 10 of 13 experiments, whereas in three experiments (nos. 10, 11 and 12), all with SACTs < 30 msec, estimation of SACT is correct. The pacemaker center in these preparations is already captured at this slow pacing rate because they show little sinus node acceleration.

At stimulation rates 10 beats/min faster than sinus rhythm, estimated values of SACT increased in general, in four preparations (nos. 9–12), all with a short SACT (< 30 msec), leading to an overestimation. However, in seven preparations with a long SACT (> 30 msec), the true values are still underestimated. All of the latter preparations showed marked sinus node acceleration, and the dominant pacemaker fibers were not captured by the atrial impulses.

Pacing at 20 beats/min faster causes a further increase in estimated SACT; the mean value (33 ± 9 msec) closely approaches true SACT. In single experiments, however, marked deviations from true SACT are observed, ranging from an underestimation of 50% (experiment 2) to an overestimation of 60% (experiment 11).

How sinus node acceleration during drive affects estimation of SACT is illustrated in figure 3. The two beats on the left are the last during a train of constant atrial pacing (interval 410 msec), followed by two spontaneous beats of sinus origin. The atrial return cycle A1A2 after cessation of drive, subtracted by the basic cycle (455 msec) and divided by two, gives an estimated SACT of 24 msec; the true SACT, however, is 58 msec. As explanation for this underestimation the microelectrode recording shows that the atrial impulses fail to capture the pacemaker fiber (smooth transition from phase 4 to phase 0 depolarization). Furthermore, the sinus node return cycle S1S2 is reduced to 412 msec with respect to the basic cycle of 455 msec, caused by an acceleration of both phase 0 depolarization and repolarization of the paced beat. Thus, sinus node acceleration accounts for the serious underestimation of SACT at slow-rate atrial pacing.

In 12 experiments, we determined the relationship between cycle length of atrial drive and CSNRT, as shown in figure 4. Panel A includes six experiments with true SACT > 30 msec. CSNRT (A1A2 – A1A1) increases continuously when the pacing cycle is shortened. Instead, the corrected recovery time of dominant fibers (S3S4 – S1S2) becomes negative (that is, the return cycle S1S2, after drive is shorter than spontaneous cycle length) due to a shortening of action potential duration. The maximum decrease of 27 ± 20 msec is reached when the atrial cycle is curtailed by 50 msec, coinciding with capture of the pacemaker center. Further curtailment slightly prolongs the CSNRT. Panel B includes six experiments with true SACT < 30 msec. As in panel A, CSNRT increased continuously when the pacing cycle was decreased. In contrast to panel A, however, the CSNRT of dominant fibers increased. The preparations exhibit less sinus node acceleration and, hence, are captured earlier during atrial drive and consequently develop a more pronounced depression of phase 4 depolarization.

Discussion

Electrotonic Interaction Between Atrium and Sinus Node

During atrial stimulation, the impulse propagates retrogradely from the atrium into the sinus node. Therefore, compared with spontaneous rhythm, depolarization and repolarization start earlier in fibers at the border of the sinus node than in fibers of the pacemaker center. Since sinus node tissue is electrically coupled,9, 10 different levels of transmembrane potentials at a given time will cause a current flow between cells tending to minimize these differences. Because of this electrotonic interaction, repolarization of dominant pacemaker fibers is accelerated compared with spontaneous rhythm. Also, a premature ectopic atrial beat penetrating the pacemaker area without capturing it nonetheless shortens action potential duration of dominant pacemaker fibers to that these fibers come to next spontaneous discharge earlier than expected; electrotonic interaction between the atrium and the sinus node during premature atrial stimulation explains why transition from compensatory to noncompensatory atrial return cycles does not indicate capture of the pacemaker center.2, 3

During constant atrial pacing, exertion of an electro-
tonic influence by the atrial wave, which either closely approaches or captures the pacemaker center, can be expected to occur with every beat. In a previous experimental microelectrode study comparing true SACT with SACT estimated by constant atrial pacing, the sinus rate accelerated during atrial pacing at a rate 5 beats/min faster than spontaneous rhythm in a minority of experiments; its mechanism remained unclear.  

Our study is the first to describe acceleration of sinus rhythm due to electrotonic interaction without capture of the pacemaker as a consistent finding during slow-rate atrial pacing. Most of the increase of sinus rate is caused by acceleration of repolarization; however, with somewhat higher pacing rates, there is also some acceleration of the process of phase 0 depolarization, until with even higher pacing rates transition from phase 4 to 0 depolarization becomes sharp, indicating capture of dominant pacemaker fibers (fig. 1). The maximal degree of sinus rate acceleration varied from preparation to preparation (table 1). It appears that the longer the true SACT, the longer the action potential duration during spontaneous rhythm, the more the electrotonic interaction presumably occurs because of the time difference of repolarization between fibers of the border and pacemaker center, all of which leads to a marked acceleration of rate, and vice versa (compare experiments 1–7 with 8–13 in table 1). Thus, if a certain pacemaker location is surrounded by very slowly conducting tissue (long SACT, long action potential duration), the acceleration of rate will be most pronounced.

In 1965, Lange12 described a temporary acceleration within the sinoatrial pacemaker of the in situ dog heart after cessation of slow-rate atrial drive. Lange also noted "the ability of an intrinsic pacemaker to continue competitive action and even to accelerate when slow extrinsic drive was attempted." Pharmacologic studies in this paper suggest that this acceleration is due to release of catecholamines from tissue storage by electrical stimulation. This mechanism of acceleration is different from our topic: Electrotonic interaction leads to acceleration up to the rate of imposed drive, but never above it, and the prior rate resumes upon cessation of drive.

The synchronization of pacemakers we report in this study is strikingly similar to the increase of atrial flutter rate in man during atrial pacing — entrainment. In both instances, the intrinsic rhythm speeds up exactly to the rate of imposed drive, and resumes its original rate upon termination of drive. It has been speculated that a reentrant atrial rhythm might similarly be accelerated by atrial pacing,15,14 which might better explain the unchanged configuration of the atrial flutter waves. If so, the phenomenon of acceleration during (and also after) electrical stimulation of the heart can be due to both an automatic and a reentrant mechanism.

Calculation of SACT by Atrial Pacing

Because of electrotonic interaction, spontaneous sinus rhythm speeds up to the rate of imposed atrial drive, until, with further increase of pacing rate, shortening of action potential duration can no longer counterbalance the shortened cycle of atrial drive, leading to capture of dominant sinus node fibers. Thus, capture of the pacemaker area by atrial pacing at rates slightly above sinus rhythm as the major prerequisite of the validity of the method is not met. This event explains the serious underestimation of true SACT when a pacing rate 5 beats/min faster than sinus rhythm is chosen (table 1). Most likely it accounts for rather low values of SACT reported in man when a rate approximately 3 beats/min faster than sinus rhythm was chosen for measurement. Narula and co-workers used a pacing rate 7 ± 3 beats/min faster than sinus rhythm (range 2–11 beats/min) and recommended a drive rate of 10 beats/min faster.4 Our study showed that with variab-

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*Figure 4. Corrected recovery time as a function of the pacing interval expressed as curtailment (basic cycle minus pacing interval). Filled circles represent the mean of corrected recovery time of the atrium plus 1 SD (A1A2–A1A4); open circles indicate the mean of corrected recovery time of a dominant pacemaker fiber – 1 SD (S2S3–S1S1). SACT = sinoatrial conduction time.*
ity from one experiment to another, seven of 13 preparations were not captured by a pacing rate 10 beats/min faster (table 1). This variability is expected to increase when diseased sinus node function in man is studied. One may argue that a pacing rate 10 beats/min faster than sinus rhythm represents a more rapid rate for overdrive at a spontaneous heart rate of 70 beats/min in man, compared to a spontaneous rate of 135 beats/min in the isolated rabbit heart. One might also speculate that with slower heart rates in man, the action potential duration of sinus node cells would be longer, disparity of repolarization between border and dominant pacemaker fibers during atrial drive larger and, hence, acceleration more pronounced. Sinus node acceleration in man cannot be predicted quantitatively, but we expect from our study that this phenomenon in man might prevent sinus node capture at pacing rates commonly used to estimate SACT.

The premature atrial stimulation and constant atrial pacing methods showed further inaccuracies, such as shortening of action potential duration of captured sinus node cells,2 differences between SACT and atrio-sinus conduction time,2,3,16 depression of diastolic depolarization and pacemaker shifts after stimulation,17,18 as previously described.11 Thus, although constant atrial pacing is simpler and quicker to perform than the premature atrial stimulation procedure, it does not improve our ability to determine sinoatrial conduction time accurately in man.

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