Cardiac Memory in Canine Atrium
Identification and Implications

Bengt Herweg, MD*; Fang Chang, PhD, MD*; Parag Chandra, MD; Peter Danilo, Jr, PhD; Michael R. Rosen, MD

**Background**—Memory is a diverse biological phenomenon whose importance in the ventricle has been demonstrated. We hypothesized its occurrence in the atrium, contributing to the modulation of cardiac rhythm.

**Methods and Results**—We analyzed P and Ta waves in conscious chronically instrumented dogs with complete heart block. Animals were atrioventricularly sequentially paced at 5% greater than the sinus rate from the lateral right atrium (RA) during control, followed by 2 periods of 1-hour test pacing at 50% greater than the sinus rate, or by equivalent test pacing from the left atrial appendage (LAA) at 5% or 50% greater than the sinus rate. Recovery RA pacing periods of 20- and 30-minute duration, respectively, succeeded each test pacing period. RA test pacing at either rate did not affect the variables measured, but changing the pacing site from RA to LAA altered the P and Ta waves. Displacement of the spatial atrial gradient vector occurred during recovery from LAA pacing, was more marked at rapid pacing rates, and manifested accumulation and resolution consistent with cardiac memory. Concurrently, the right effective refractory period decreased.

**Conclusions**—Memory is demonstrable in canine atrium, showing rapid onset, accumulation during successive pacing periods, and resolution on cessation of pacing. Given its association with a reduced effective refractory period, it may contribute to the substrate for atrial arrhythmias. (Circulation. 2001;103:455-461.)

**Key Words:** electrophysiology ■ pacing ■ atrium ■ remodeling

Cardiac memory is a T-wave change that follows ventricular pacing, ventricular arrhythmia, preexcitation, or intermittent left bundle-branch block. Characteristic of memory are accumulation of T-wave changes, their augmentation with repeated episodes of altered ventricular activation, and their resolution over periods that depend on the duration of the inciting stimulus.

Memory has not been described in the atrium, but the potential importance of spatially heterogeneous action potential (AP) duration and refractoriness and their remodeling by rapid atrial pacing or tachycardia has been long recognized. Moreover, the concept that “atrial fibrillation begets atrial fibrillation” implies a kind of atrial memory, although memory was not demonstrated in studies using atrial monophasic AP recordings in Langendorff-perfused rabbit hearts.

Because memory is a property common to diverse tissues and because the negative studies of atrial memory have been performed only in isolated perfused hearts, we elected to analyze P and Ta waves in conscious dogs to test whether memory is present. In so doing, we measured changes in the same variable (the T wave) that is the standard descriptor of memory in the ventricle. We considered this a direct means to evaluate in the atrium the criteria of Rosenbaum et al for cardiac memory. We demonstrate that memory is present and reflects the plasticity of atrial electrophysiological properties, and we discuss its potential contributions to cardiac rhythm modulation.

**Methods**

**Animal Preparation**

The present study conformed with the rules of the Columbia University Institutional Animal Care and Use Committee. Six 24- to 26-kg mongrel dogs were anesthetized with thiopental sodium (17 mg/kg IV) and ventilated with isoflurane (1.5% to 2%) and O₂ (2 L/min). Morphine sulfate (0.15 mg/kg) was injected epidurally for postoperative analgesia. By use of sterile techniques, a right intercostal thoracotomy was performed, and the heart was suspended in a pericardial cradle. Bipolar Medtronic electrodes (model 5058) were attached epicardially to the left atrial (LA) appendage (LAA) and right ventricular free wall. Leads were tunnelled subcutaneously and connected to a Medtronic 7864B dual-chamber pulse generator implanted in the right posterior thorax. Bipolar electrodes for pacing, recording electrograms, and measuring effective refractory periods (ERP) were attached to the lateral right atrium (RA) and LAA, subcutaneously tunneled to the right posterior thorax, and exterior-
ized. Complete heart block was produced by injecting 0.1 to 0.3 mL of 40% formaldehyde into the basal ventricular septum.9

Immediately after surgery, the pulse generator was programmed into a VDD mode (rate limits 30 and 150 bpm, sensed atrioventricular [AV] delay 80 ms). This ensured P-synchronous ventricular pacing with a normal PR interval during recovery, thus maintaining a sinus-initiated rhythm and avoiding any atrial remodeling secondary to the AV dyssynchrony that characterizes heart block. Dogs were monitored and stabilized for ~3 weeks, at which time recovery was complete, the ECG was stable (ie, sinus rhythm with ventricular pacing), and the animals were laboratory-trained.

Experimental Protocol

Figure 1 shows the experimental protocol. Experiments were performed on conscious animals resting quietly on their left sides. Experimental pacing was performed with a Bloom DTU 210 stimulator via the bipolar electrodes on the RA and the LAA.

Protocol 1 tested effects of altered cardiac activation on P and Ta waves. During control, the paced AV delay of 220 ms permitted visualization of Ta waves. P and Ta waves achieved equilibrium during AV sequential pacing from the RA electrode at ~5% greater than the sinus rate (111±4 bpm). Control was followed by two 60-minute periods of test pacing from the LAA at 111±4 bpm. Pacing stimuli were 2-ms square waves at twice threshold current. Each LAA pacing period was followed by recovery periods of RA pacing of 20-minute (recovery 1) and 30-minute (recovery 2) duration. The AV interval and ventricular pacing rate were constant throughout each experiment.

Protocol 2 assessed the influence of altered atrial rate but not activation. Control and recovery RA pacing were as described above (~5% greater than the sinus rate). However, pacing for the 60-minute test periods was now delivered from the RA electrode at ~50% greater than the sinus rate (pacing rate 160±0 bpm). Control was followed by two 60-minute periods of test pacing from the LAA at 111±4 bpm. Pacing stimuli were 2-ms square waves at twice threshold current. Each LAA pacing period was followed by recovery periods of RA pacing of 20-minute (recovery 1) and 30-minute (recovery 2) duration. The AV interval and ventricular pacing rate were constant throughout each experiment.

Protocol 3 determined the summed effects of altered rate and activation on P and Ta waves. Protocol 3 was identical to protocol 1, except that the two 60-minute periods of LAA test pacing were ~50% greater than the sinus rate (160±0 bpm). The ventricle was stimulated after every second atrial beat during rapid atrial pacing periods to maintain a physiological ventricular rate. No other above-described parameter was changed.

Protocol 3 determined the summed effects of altered rate and activation on P and Ta waves. Protocol 3 was identical to protocol 1, except that the two 60-minute periods of LAA test pacing were ~50% greater than the sinus rate (160±0 bpm). The ventricle was stimulated after every second atrial beat as in protocol 2.

Electrophysiological Study

Activation time was the interval between atrial pacing artifacts and dV/dt max of RA and LAA electrograms at basic cycle lengths of 400, 300, and 200 ms. ERP was measured by introducing single extra-stimuli via the RA electrode after 10-beat drive trains at basic cycle lengths of 400, 300, and 200 ms. Basic (S1) and premature (S2) stimuli were 2-ms square waves delivered at twice threshold current, with S1-S2 decrements of 2 ms. The ERP was the longest S1-S2 interval that failed to produce a propagated response, manifested as a P wave on ECG. ERPs were determined early in the initial control period and after recovery 2.

**Figure 1.** Experimental protocol.

![Experimental protocol diagram](Image)

![Figure 1](Image)

**Figure 2.** Signal-averaged P and Ta waves in orthogonal lead X during AV sequential pacing. Complete AV block allowed sufficient AV interval prolongation to reveal the entire Ta wave (left). Amplification (right) permitted accurate measurement of amplitudes, intervals, and isoareas.

Data Recording and Analysis: ECG Theory and Method

P and Ta waves sum all potential differences during atrial activation and repolarization over time. If atrial recovery properties were uniform, the Ta-wave area should equal the P-wave area. However, ERP measurements, reflecting repolarization, indicate that atrial recovery is not uniform (ie, ERP is greater in the RA than in the LA). This dispersion of repolarization reflects cellular properties intrinsic to particular loci, theoretically should not depend on activation, and might be interpreted as inducing a primary Ta wave (ie, generated by the intrinsic molecular and ionic properties of myocytes, independent of activation). However, also contributing to Ta waves are the dispersion of activation across RA and LA, creating voltage gradients among phase-shifted APs and contributing to what is effectively a secondary Ta wave. Therefore, the Ta wave may be a function of both AP onset and duration, combining characteristics of primary (dependent on local recovery properties) and secondary (dependent on activation) repolarization.

By studying animals in complete heart block, we prolonged PR intervals sufficiently to completely reveal P and Ta waves (Figure 2, left). As expected, the end of depolarization and the onset of recovery overlap11 such that there is no isoelectric ST segment in the atrial ECG. This is consistent with earlier studies showing P- and Ta-wave discordance during sinus rhythm and pacing (PTa angle θ=170° to 180°).12,13 In contrast, in the ventricle, QRS- and T-wave polarities are similar. Ventricular QRS-T wave concordance (QRS-T angle 20±18°)12 can be explained by opposing pathways of ventricular depolarization and repolarization.

Recordings were acquired over a Frank lead system with a Mida 1000 (Ortivus) acquisition system that facilitated signal-averaging 3D P- and Ta-wave vectorcardiograms. Data were analyzed by use of Mida 1200 and 1000 Ortivus software. Left, inferior, and anterior directions of X-, Y-, and Z-axes were considered positive. As shown in Figure 2, we measured PTa intervals (the longest PTa interval in X, Y, or Z leads), and P and Ta wave amplitudes, allowing calculation of XYZ PTa dispersion, spatial root-mean-square (RMSQ) P and Ta vector amplitudes, and spatial displacement of P- and Ta-wave vectors. Examples of these calculations for the P wave are as follows:

- **RMSQ P-wave amplitude**
  \[ \text{RMSQ P-wave amplitude} = \sqrt{(\text{amp P}_x)^2 + (\text{amp P}_y)^2 + (\text{amp P}_z)^2} \]
  
- **Spatial P-wave displacement**
  \[ \text{Spatial P-wave displacement} = \sqrt{(\text{amp P-P}_x)^2 + (\text{amp P-P}_y)^2 + (\text{amp P-P}_z)^2} \]

where \(\text{amp P}\) indicates P-wave amplitude. Measurements of XYZ isoareas of P and Ta waves allowed for the determination of P and PTa voltage-time integrals (arithmetic sum of P and Ta isoareas) and their RMSQ values.12,13 We also adopted earlier methods4 to quantify...
dent of the activation sequence, and local ventricular recovery of repolarization. These observations suggest that (1) changes in properties and ERP are modified instantaneously with changes in the activation sequence associated with secondary repolarization or (2) QRST waves should equal the PTa voltage-time integral in X, Y, and Z leads comparing RA and LAA pacing; Ta-wave changes occur. In contrast, there is no change in P and Ta amplitudes in any lead or in PTa angle or interval while varying the rate with RA pacing (data not shown).

Statistical Analysis

Data were analyzed by use of SPSS 8.0 software and expressed as mean±SEM. Repeated-measures ANOVA was used to compare multiple sequential measurements. Post hoc multiple comparisons were performed by the method of Bonferroni where equal variances were assumed, and the Games-Howell method was used where variances were not equal. A value of P<0.05 was considered significant.

Results

P- and Ta-wave amplitudes are inversely correlated (r=0.73, P<0.001), and pacing-induced P wave changes result in the Ta changes shown in Figure 3. Thus, the atrium manifests secondary Ta waves. With alteration of the stimulation site, P and Ta displacements are reciprocal, maintaining spatial opposition in all leads (Figure 3, right). Ta displacement is directly proportional to P-wave displacement (r=0.87, P<0.001) and is most pronounced in lead X (oriented along the axis of altered activation).

Results from Protocol 1

Representative ECG recordings of P and Ta waves and related PTa vector loops and gradients from 1 dog are displayed respectively in Figure 4. Altered P-wave morphology is achieved on changing the stimulation site from RA to LAA, and this is associated with an altered Ta wave (Figure 4A). During recovery periods 1 and 2 (after terminating LAA pacing), P waves widen in lead X, and Ta waves approach more positive voltages in lead X and more negative voltages in leads Y and Z. Ta changes are more pronounced in recovery 2 than in recovery 1 (consistent with accumulation), and partial resolution occurs late in recovery 2.

P vector loops during RA pacing are wider in horizontal and sagittal planes than in the frontal plane, and P and Ta loops are markedly altered during LAA pacing (Figure 4B). The Ta vector in recovery 1 shifts toward the P wave inscribed during LAA pacing and shifts even more so in recovery 2 (accumulation). AGs manifest a change in Ta that resolves in the first, but not in the second, postspacing period (Figure 4C). Hence, with LAA pacing, concurrent P- and Ta-wave changes occur. In contrast, there is no change in P and Ta amplitudes in any lead or in PTa angle or interval while varying the rate with RA pacing (data not shown). Table 1 summarizes selected data showing significant changes in P and Ta amplitudes during LA pacing (data not shown).
recovery 1 or 2. When activation alone was changed by pacing from LAA, a modest change in spatial AG occurred. However, when rapid LAA pacing was performed, accumulation of change in AG during recoveries 1 and 2 occurred. This is consistent with cardiac memory.

Dispersion of Repolarization and Changes in ERP
During recovery 1, XYZ PTa-interval dispersion was unstable. It decreased significantly in recovery 2 and then resolved (Figure 9). ERP was measured in protocol 1 only (Table 2) and was shortened at all cycle lengths. Moreover, the ERP/PTa ratio decreased significantly, suggesting that the effect on ERP might be arrhythmogenic.

Discussion
Atrial memory is characterized by an increase of the PTa voltage-time integral along the axis of transiently altered activation, resulting in displacement of the spatial AG vector. Accumulation occurs after the second period of altered activation and is followed by resolution. These cumulative perturbations in atrial repolarization after transient alteration of the activation pathway not only satisfy previously defined criteria for cardiac memory but are accompanied by decreased XYZ PTa dispersion and decreased RA ERP.

Other investigators have not demonstrated memory in the atrium. Wood et al defined memory in the atria of Langendorff-perfused rabbit hearts in light of the inverse relationship between activation time and AP duration at 90% repolarization at a monophasic AP recording site. The discrepancy between their results and our results may have several explanations as follows: Because the magnitude of change in atrial vectors is far smaller than that characterizing the ventricle, more sensitive techniques may be required to study atrial memory. In this light, measuring activation time and monophasic AP duration at 90% repolarization may be insufficiently sensitive or stable or may represent just part of the spectrum of changes seen with memory, whereas use of orthogonal XYZ recordings may allow more complete appreciation of the relationship between repolarization changes and preceding alterations in the activation pathway. Moreover, compared with rabbit atrium, the canine atrium manifests changes in a greater mass of tissue expressed over longer distances, which should facilitate recording any memory present. It is also possible that in the rabbit studies, abnormal atrial activation was not achieved and/or that rabbit atrium does not manifest memory.
As is the case for pacing to induce memory in the ventricle, the changes observed during recovery from LA pacing appear to affect repolarization primarily and are expressed electrocardiographically as an altered PTa voltage-time integral in the absence of altered P-wave amplitude or duration and the P voltage-time integral. This result suggests that changes in local repolarizing currents and AP durations are elements of atrial memory and are consistent with memory in the ventricle. Yet, in contrast to ventricular T-wave memory, that in the atrium is not manifested dramatically on standard surface ECG leads. This may be explained by the differences between atrial and ventricular activation and repolarization, likely resulting from anatomic and electrophysiological differences in the conduction systems of the respective chambers. Atria are activated rather sequentially during sinus rhythm or pacing, creating a large transatrial gradient during activation and repolarization, and atrial repolarization is significantly influenced and determined by atrial activation (Figure 3). Hence, a portion of the Ta-wave amplitude is likely generated by temporal dispersion of AP onset in both atria, whereas a

<table>
<thead>
<tr>
<th>TABLE 1. Sample Measurements of Vector/ECG Parameters</th>
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<tbody>
<tr>
<td>Activation (n=6)</td>
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<tr>
<td>------------------</td>
</tr>
<tr>
<td>P amplitude</td>
</tr>
<tr>
<td>X, µV</td>
</tr>
<tr>
<td>Y, µV</td>
</tr>
<tr>
<td>Z, µV</td>
</tr>
<tr>
<td>RMSQ P amplitude, µV</td>
</tr>
<tr>
<td>Ta amplitude</td>
</tr>
<tr>
<td>X, µV</td>
</tr>
<tr>
<td>Y, µV</td>
</tr>
<tr>
<td>Z, µV</td>
</tr>
<tr>
<td>RMSQ Ta amplitude, µV</td>
</tr>
<tr>
<td>PTa angle</td>
</tr>
<tr>
<td>P displacement, µV</td>
</tr>
<tr>
<td>Ta displacement, µV</td>
</tr>
<tr>
<td>PTa interval, ms</td>
</tr>
<tr>
<td>P-wave duration, ms</td>
</tr>
<tr>
<td>Local activation time at LAA, ms</td>
</tr>
</tbody>
</table>

Values are mean±SEM. *P<0.05 compared with control RA pacing. †At RA.

Figure 5. PTa voltage-time integrals during recovery 1 and recovery 2 after LAA pacing compared with control (C). *P<0.05. Control PTa voltage-time integral values in X, Y, and Z leads were 1.05±0.82, 3.10±0.45, and 2.44±0.50 µV·sec, respectively (n=6).

Figure 6. Spatial AG vector (µV·sec) constructed 3-dimensionally by using XYZ PTA voltage-time integrals as coordinates. AG vectors in control (C), recovery 1 at 1 minute (R1), and recovery 2 at 1 minute (R2) are shown. Subsequent time points are white (recovery 1) and black (recovery 2). Spatial displacement of AG vector during R1 and R2 compared with control demonstrates accumulation and resolution. Solid vertical lines facilitate orientation of data points on Z-axis. *P<0.05 vs control.
that altered sites of atrial impulse origin and/or activation pathways are sufficient to remodel the atrium electrophysiologically. During rapid LAA pacing (remembering that rapid rate originating near the sinus node has no protracted effects), even greater accumulation of changes in atrial gradient is seen. In other words, when abnormal activation is more frequent, the resultant change is of greater magnitude and persistence. Moreover, the results of pacing in this fashion are accompanied by changes in dispersion of repolarization and ERP that would facilitate propagation of premature impulses, increasing the likelihood of arrhythmogenesis.

These findings are important in our consideration of atrial remodeling as a facilitator of atrial tachyarrhythmias and fibrillation. They highlight the importance of the site of impulse origin and of activation pathways. Although fibrillation can be achieved by rapid right atrial pacing ($\approx 400$ bpm),\textsuperscript{4–6} our results suggest that it may well be that altered atrial activation over a wide range of rates is a key contributor to the arrhythmogenic substrate.

The mechanisms responsible for atrial memory are not known. In the ventricle, the changed stress-strain relationships induced by altered pathways of activation induce

### TABLE 2. Activation Times, ERP, PTa Interval, and ERP/PTa Ratio During Pacing From Lateral RA at Control and Recovery 2 (30 Min) in Protocol 1

<table>
<thead>
<tr>
<th>Basic Drive Cycle Length</th>
<th>Control</th>
<th>400 ms</th>
<th>300 ms</th>
<th>200 ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activation time, ms</td>
<td>73.8±5.1</td>
<td>72.5±5.2</td>
<td>74.4±5.3</td>
<td></td>
</tr>
<tr>
<td>ERP, ms</td>
<td>147.4±4.0*</td>
<td>137.8±4.6</td>
<td>125.2±3.9</td>
<td></td>
</tr>
<tr>
<td>PTa interval, ms</td>
<td>216±6*</td>
<td>207±10*</td>
<td>182±4</td>
<td></td>
</tr>
<tr>
<td>ERP/PTa ratio</td>
<td>0.70±0.01</td>
<td>0.70±0.02</td>
<td>0.70±0.02</td>
<td></td>
</tr>
<tr>
<td>Recovery 2 (30 min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activation time, ms</td>
<td>72.9±5.4</td>
<td>72.9±5.7</td>
<td>74.3±5.8</td>
<td></td>
</tr>
<tr>
<td>ERP, ms</td>
<td>137.5±5.3*</td>
<td>129.6±2.8*</td>
<td>120.4±1.6*</td>
<td></td>
</tr>
<tr>
<td>PTa interval, ms</td>
<td>213±7*</td>
<td>204±7*</td>
<td>182±4</td>
<td></td>
</tr>
<tr>
<td>ERP/PTa ratio</td>
<td>0.66±0.02*</td>
<td>0.65±0.02*</td>
<td>0.68±0.01*</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean±SEM. Activation time was measured to LAA.

\*P<0.05 vs 200-ms basic drive cycle length; †P<0.05 vs control.
memory that is prevented by interfering with angiotensin II synthesis or binding. Sadoshima et al demonstrated that cardiac cell cultures exposed to altered stress/strain synthesized increased angiotensin II. Given these results, we propose that when the site of atrial impulse initiation is altered, the changed stress-strain relationships would initiate a similar signal transduction pathway. In the ventricle, there is an association of endothelin-derived signaling processes with short-term memory, another factor requiring study in the atrium. Finally, both vagal and sympathetic neurohumoral actions need be considered.

In conclusion, we have demonstrated changes in AG that persist after a period of transiently altered atrial activation. These changes are maximal along the axis of transiently altered activation and are likely consequences of altered atrial recovery properties. Accumulation of these changes occurs after a second period of transiently altered activation, after which partial resolution takes place. Thus, we conclude that short-term memory exists in the atrium. The questions of whether long-term memory also occurs and whether and how such atrial memory relates to initiation and perpetuation of arrhythmias remain to be answered.

Acknowledgments

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