Repolarization Changes Underlying Long-Term Cardiac Memory Due to Right Ventricular Pacing
Noninvasive Mapping With Electrocardiographic Imaging

Scott B. Marrus, MD, PhD; Christopher M. Andrews, BS; Daniel H. Cooper, MD; Mitchell N. Faddis, MD, PhD; Yoram Rudy, PhD

Background—Cardiac memory refers to the observation that altered cardiac electrical activation results in repolarization changes that persist after the restoration of a normal activation pattern. Animal studies, however, have yielded disparate conclusions, both regarding the spatial pattern of repolarization changes in cardiac memory and the underlying mechanisms. The present study was undertaken to produce 3-dimensional images of the repolarization changes underlying long-term cardiac memory in humans.

Methods and Results—Nine adult subjects with structurally normal hearts and dual-chamber pacemakers were enrolled in the study. Noninvasive electrocardiographic imaging was used before and after 1 month of ventricular pacing to reconstruct epicardial activation and repolarization patterns. Eight subjects exhibited cardiac memory in response to ventricular pacing. In all subjects, ventricular pacing resulted in a prolongation of the activation recovery interval (a surrogate for action potential duration) in the region close to the site of pacemaker-induced activation from 228.4±7.6 ms during sinus rhythm to 328.3±6.2 ms during cardiac memory. As a consequence, increases are observed in both apical-basal and right-left ventricular gradients of repolarization, resulting in a significant increase in the dispersion of repolarization.

Conclusions—These results demonstrate that electrical remodeling in response to ventricular pacing in human subjects results in action potential prolongation near the site of abnormal activation and a marked dispersion of repolarization. This dispersion of repolarization is potentially arrhythmogenic and, intriguingly, was less evident during continuous right ventricular pacing, suggesting the novel possibility that continuous right ventricular pacing at least partially suppresses pacemaker-induced cardiac memory. (Circ Arrhythm Electrophysiol. 2012;5:773-781.)

Key Words: action potentials ▪ cardiac memory ▪ pacemakers ▪ remodeling ▪ T-wave memory

Cardiac electrical remodeling occurs in response to a variety of situations, including heart failure, atrial fibrillation, and altered rate or pattern of activation. It is well established that periods of abnormal ventricular activation result in changes in myocardial repolarization, manifested by a persistent change in T-wave axis after restoration of normal cardiac excitation. Rosenbaum et al (as well as other researchers) have defined several key features of this phenomenon, including the facts that the degree and persistence of the T-wave changes depended on the duration of abnormal excitation and that T-wave memory exhibits accumulation. These changes are reminiscent of memory in the central nervous system, and thus the term cardiac memory was introduced.

Clinical Perspective on p 781

In their seminal study of the phenomenology of cardiac memory, Rosenbaum et al noted that the altered T-wave axis in cardiac memory recapitulated the paced QRS axis, suggesting that, after restoration of normal activation, repolarization is delayed in the region closest to the site of ectopic activation. This hypothesis received further support from canine studies in which epicardial pacing resulted in a prolongation of epicardial action potentials (as measured in both single isolated cells and from tissue strips). Studies performed in intact canine hearts using unipolar electrograms to measure local activation and recovery time (RT) also demonstrated delayed epicardial repolarization near the location of the pacing site. In contrast, using optical mapping of transmural canine wedge preparations, Jeyaraj et al demonstrated action potential prolongation in the region most distant from the pacing site. These disparate results, in addition to the repolarization changes that were the focus of most studies of cardiac memory, studies in the intact canine heart have suggested that delayed epicardial activation also contributes to cardiac memory. These disparate results,
likely reflecting different experimental systems, highlight the importance of examining cardiac memory in vivo.

Several studies have suggested that altered mechanical strain during abnormal cardiac activation is the signal that results in electrical remodeling. In a Langendorff-perfused rabbit heart model, global alterations in strain resulted in altered expression of cardiac memory and, intriguingly, local mechanical strain sufficed to induce T-wave changes similar to those of cardiac memory. During right ventricular (RV) apical pacing, myocardial strain and workload are increased in regions most distant from the site of pacing and reduced near the site of pacing. In addition, early-activated regions also displayed reduced perfusion and oxygen uptake. A hypothesis from these observations is that heterogeneous changes in strain and workload underlie cardiac memory; however, whether the electrical changes correspond to regions of increased strain (distant from the pacing site) or reduced strain and reduced perfusion (close to the pacing site) remains a crucial and unresolved issue.

To further clarify the mechanism of cardiac memory in the human heart, we undertook the current study to determine the spatial pattern of electrical changes underlying the body surface T-wave inversions of cardiac memory. To address this question, we used the novel electrocardiographic imaging (ECG imaging) methodology that allows reconstruction of epicardial activation and recovery patterns in patients with dual-chamber pacemakers before and after the induction of cardiac memory.

Methods

Subject Enrollment

Nine adult subjects were enrolled in the study. Enrollment criteria included prior implantation of a dual-chamber pacemaker, normal cardiac function, no history of valvular abnormalities or coronary artery disease, no prior percutaneous coronary interventions or surgical cardiac procedures, and minimal burdens of atrial fibrillation or ventricular pacing. All subjects provided written, informed consent, and all protocols were reviewed and approved by the Human Research Protection Office at Washington University School of Medicine.

Electrocardiographic Imaging

The electrocardiographic imaging methodology has been previously described. Briefly, body surface electrical data were acquired at 2 kHz using a 256-lead body surface mapping system (Biosemi). After electrode application, subjects underwent noncontrast thoracic gated computed tomography scans, with an axial resolution of 3 mm. Scans were gated at 70% of the R-R interval. Epicardial and body surface geometry were labeled and digitized from computed tomography images using Amira (Visage Imaging). The body surface potentials and geometric information were combined using the electrocardiographic imaging algorithms in MATLAB (MathWorks, Natick, MA) to reconstruct epicardial potentials and unipolar electrograms.

Analysis

The raw data set consisted of reconstructed unipolar epicardial electrograms for 512 nodes on the epicardial surface. Local activation time (AT) for each node was defined as the time of minimal dV/dt during the local QRS complex; local RT for each node was determined using the traditional Wyatt method (the time of maximal dV/dt during the local T wave). The local activation-recovery interval (ARI) was calculated for each node as the difference between the onset of the QRS complex to the end of the T wave and multiplying by the sampling interval. For each subject, 4 consecutive beats were reconstructed and analyzed; the local AT, RT, and ARI at each node during each beat were then averaged. The epicardial surface was divided into 18 regions (basal, mid, and apical segments for anterior, lateral, and inferior regions of both the RV and left ventricle [LV]). Regions were assigned without visualization of either activation or recovery patterns. For each subject, all nodes within each region were averaged together.

Statistics

Within each cardiac region, each parameter (AT, RT, ARI, and QRST integral) was analyzed across pacing conditions using a repeated measures 1-way ANOVA, followed by post hoc tests with a Bonferroni correction. Comparisons between baseline (normal sinus rhythm [NSR]) and the onset of RV pacing, between the onset of RV pacing and after 1 month of RV pacing, and between baseline and after cessation of RV pacing (ie, cardiac memory) were prespecified for the purpose of post hoc analyses. No correction was made for repeated analyses in different cardiac regions. Apical-basal gradients were calculated in each subject between anterior apical LV and anterior basal LV; RV-LV gradients were calculated between midlateral RV and midlateral LV. Statistical analyses were carried out using Prism 5 (GraphPad Software Inc, La Jolla, CA).

Results

Subjects and Study Design

The clinical characteristics of the participants are summarized in Table 1. All subjects had dual-chamber cardiac pacemakers implanted for sick sinus syndrome (n=7), a history of transient atrioventricular block (n=1), or neurocardiogenic syncope with a prominent cardioinhibitory component (n=1) and no history of coronary, valvular, or other structural cardiac disease. One subject had a previous radiofrequency ablation procedure in the left atrial appendage for atrial fibrillation ablation.

Table 1. Summary of Clinical Characteristics of Study Participants

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Sex</th>
<th>Cardiac Diagnoses</th>
<th>Cardiac Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44</td>
<td>Male</td>
<td>Sick sinus syndrome</td>
<td>Propanolol</td>
</tr>
<tr>
<td>2</td>
<td>56</td>
<td>Female</td>
<td>Neurocardiogenic/cardioinhibitory syncope</td>
<td>Metoprolol</td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>Female</td>
<td>Sick sinus syndrome</td>
<td>Enalapril</td>
</tr>
<tr>
<td>4</td>
<td>72</td>
<td>Male</td>
<td>Sick sinus syndrome, s/p atrial flutter ablation</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>Female</td>
<td>Sick sinus syndrome</td>
<td>Aspirin</td>
</tr>
<tr>
<td>6</td>
<td>77</td>
<td>Female</td>
<td>Sick sinus syndrome</td>
<td>Metoprolol XL</td>
</tr>
<tr>
<td>7</td>
<td>51</td>
<td>Female</td>
<td>h/o Mobitz 2, type 1 AV block</td>
<td>Sotalol</td>
</tr>
<tr>
<td>8</td>
<td>52</td>
<td>Male</td>
<td>Sinus bradycardia</td>
<td>Aspirin</td>
</tr>
<tr>
<td>9</td>
<td>63</td>
<td>Male</td>
<td>Sick sinus syndrome, s/p atrial fibrillation ablation</td>
<td>Sotalol</td>
</tr>
</tbody>
</table>

HCTZ indicates hydrochlorothiazide; s/p, status post; h/o, history of; AV, atrioventricular.
for atrial flutter, and 1 had a previous radiofrequency ablation for atrial fibrillation; none had a history of ventricular arrhythmias or ventricular ablations. At baseline, the subjects required minimal ventricular pacing (3.2±1.3%). However, 1 subject (subject 8) exhibited an unexpected 20% ventricular pacing at the first study-related visit and was excluded from further analysis. Interestingly, we noted that this subject displayed, at the first visit, the same repolarization changes recorded in the other participants after 1 month of ventricular pacing (discussed below), suggesting that substantially <100% ventricular pacing suffices to induce cardiac memory.

Subjects underwent baseline electrocardiographic imaging during supraventricular activation (either NSR or atrial pacing) after which the pacemaker was reprogrammed with a short atrioventricular delay, determined by maximizing the width of the body surface QRS. Pacemaker parameters for each subject are summarized in Table 2; on average, the paced atrioventricular delay was 128±8 ms and the sensed atrioventricular delay was 101±7 ms. These settings achieved nearly 100% ventricular pacing during supraventricular activation (either NSR or atrial pacing); it requires further study. The remaining analysis focuses on the epicardial electrical changes associated with cardiac memory in the 7 participants with body surface T-wave inversions.

Table 2. Pacemaker Parameters for Study Participants

<table>
<thead>
<tr>
<th>Subject</th>
<th>Baseline VP, %</th>
<th>Baseline AP, %</th>
<th>Paced AV Delay, ms</th>
<th>Sensed AV Delay, ms</th>
<th>VP During Study, %</th>
<th>AP During Study, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.8</td>
<td>10.1</td>
<td>110</td>
<td>80</td>
<td>100</td>
<td>13.7</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>86</td>
<td>110</td>
<td>80</td>
<td>100</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>96</td>
<td>150</td>
<td>120</td>
<td>94.5</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>1.9</td>
<td>99</td>
<td>160</td>
<td>130</td>
<td>98</td>
<td>97.9</td>
</tr>
<tr>
<td>5</td>
<td>0.3</td>
<td>36.4</td>
<td>120</td>
<td>100</td>
<td>99.9</td>
<td>27.6</td>
</tr>
<tr>
<td>6</td>
<td>1.4</td>
<td>95.8</td>
<td>120</td>
<td>100</td>
<td>99.2</td>
<td>96</td>
</tr>
<tr>
<td>7</td>
<td>1.5</td>
<td>1.1</td>
<td>150</td>
<td>120</td>
<td>99.1</td>
<td>4.2</td>
</tr>
<tr>
<td>8</td>
<td>20</td>
<td>31</td>
<td>120</td>
<td>80</td>
<td>97</td>
<td>53</td>
</tr>
<tr>
<td>9</td>
<td>3.8</td>
<td>1.4</td>
<td>100</td>
<td>80</td>
<td>99.8</td>
<td>1.6</td>
</tr>
</tbody>
</table>

VP indicates ventricular paced; AP, atrial paced; AV, atrioventricular.

Figure 1. Epicardial electrograms exhibit localized regional T-wave inversions after right ventricular (RV) pacing. Representative electrocardiograms demonstrate body surface T-wave inversions in lead V2, which mirror the QRS complex present during RV pacing. Similarly, the epicardial electrogram from the apical-lateral RV exhibits T-wave inversion after RV pacing, whereas the epicardial electrogram from the basal lateral left ventricle (LV) does not exhibit changes after RV pacing. Scale bar, 250 ms. NSR indicates normal sinus rhythm.

The entire study, therefore, comprises 4 sequential electrocardiographic imaging conditions: (1) baseline (either NSR or atrial pacing—henceforth referred to as NSR for simplicity), (2) onset of ventricular pacing, (3) ventricular pacing after 1 month of pacing, and (4) after restoration of either NSR or atrial pacing (henceforth referred to as cardiac memory for simplicity, although evidence of cardiac memory remodeling is evident during pacing, as discussed below). To eliminate any possible effects of activation pattern on the intrinsic repolarization indices (ARI and QRST integral), we confined the repolarization analysis to comparisons during the same activation pattern.

**Body Surface and Epicardial T-Wave Changes**

As has been reported previously, NSR after a period of RV pacing was associated with the development of body surface T-wave inversions that mirror the QRS axis of RV pacing (Figure 1).1,3,5 In the present study, 7 of 8 participants developed body surface T-wave inversions indicative of cardiac memory. Interestingly, the RV lead in the 1 participant without T-wave inversions was implanted in a high septal location, whereas the other 7 participants had an RV apical lead placement; whether this contributed to the lack of cardiac memory requires further study. The remaining analysis focuses on the epicardial electrical changes associated with cardiac memory in the 7 participants with body surface T-wave inversions.

Inspection of epicardial electrograms revealed that epicardial T waves exhibited behavior similar to body surface T waves, ie, becoming inverted in regions with a negative epicardial QRS complex during pacing. Specifically, epicardial T-wave inversions were evident during cardiac memory in the apical-lateral RV but not in the basal-lateral LV (Figure 1).

**Activation Patterns**

In all patients, the epicardial activation pattern during NSR was characterized by a broad activation breakthrough on the RV free wall followed by rapid activation of the ventricular surface, with the latest activation occurring at the LV base, as was described previously for normal subjects17 (Figure 2A); on average, this RV breakthrough occurred 16.5±2.2 ms after the onset of the body surface QRS (all time points are in reference to the onset of the body surface QRS). During RV pacing, a smaller focus of early activation typically appeared over the RV apex (Figure 2B and 2C); the earliest epicardial activation during RV pacing occurred at 10.7±2.1 ms (P=0.31 compared with earliest AT during NSR). In contrast to the relatively subtle changes in earliest AT, the time of latest epicardial activation was markedly different during RV pacing. RV pacing delayed the time of latest epicardial activation (located in the basal-lateral LV) from 66.6±2.9 to 123.7±6.7 ms (P<0.001).
During cardiac memory, both the times of earliest (21.9±3.9 ms) and latest (70.4±2.4 ms) epicardial activation did not differ from baseline earliest (16.5±2.2 ms) and latest (66.6±2.9 ms) epicardial activation ($P=0.39$ for earliest AT and $P=1.86$ for latest AT). The mean AT of apical-lateral RV was unchanged after ventricular pacing (41.5±1.8 ms versus 40.6±2.2 ms; $P=2.49$) as was the AT of the basal-lateral LV (52.6±2.9 ms versus 55.1±4.1 ms; $P=2.14$). In addition, visual inspection of the pattern of epicardial activation did not suggest a change in the overall pattern of epicardial activation after the induction of cardiac memory (Figure 2D). Taken together, these results indicate that cardiac memory does not result in persistent changes in the epicardial activation pattern.

**Recovery Pattern**

After cessation of RV pacing, there was a slight delay in the earliest RT (from 200.5±8.7 ms during NSR to 226.1±11.7 ms during cardiac memory; $P=0.045$) and no significant change in the latest RT (383.3±30 ms during NSR versus 412.5±17.3 ms during cardiac memory; $P=0.30$). There were, however, marked local changes in recovery pattern, specifically a region of delayed recovery over the RV (Figure 3A and 3B). Although the exact extent of this delayed region varied from subject to subject, it was invariably centered over the site of earliest pacemaker-induced activation (Figure 3C). In the apical-lateral RV, the mean±SEM RT was delayed from 265.4±9.5 ms during NSR to 371.2±16.6 ms after restoration of NSR ($P<0.001$). In contrast, no significant changes in RT occurred in the basal-lateral LV as a result of RV pacing (294.9±15.5 ms during NSR versus 301.2±12.0 ms after RV pacing; $P=1.93$). Importantly, every subject with evidence of body surface T-wave memory exhibited a delayed apical-lateral RV RT after RV pacing but no significant change in basal-lateral LV RT (Figure 3D and 3E).
Activation-Recovery Intervals
The difference between local AT and local RT is termed the ARI and serves as a surrogate for local action potential duration (APD). Several previous studies have confirmed that ARI correlates closely with APD under a variety of conditions. A significant prolongation of the local ARI occurred in the apical-lateral RV as a consequence of RV pacing (228.4±7.6 ms during NSR versus 328.3±6.2 ms during cardiac memory; \(P<0.001\)). In contrast, no significant ARI change occurred in the basal-lateral LV (248.2±11.7 ms during NSR versus 245.2±7.5 ms during cardiac memory; \(P=2.08\)). Although the precise size and location of the region of ARI prolongation varied slightly between subjects, there was a clear relationship between the region of early, pacemaker-induced activation and the region that exhibited ARI prolongation after the cessation of pacing (Figure 4).

Gradients of Repolarization Underlying T-wave Inversions
As discussed above, altered repolarization gradients in any axis could theoretically affect the body surface T wave. Both the apical-basal and RV-LV gradients in RT became significantly greater after induction of cardiac memory (apical-basal gradient, −3.7±6.7 ms during NSR versus 36.0±16.7 ms during cardiac memory; \(P=0.017\); RV-LV gradient, −18.9±10.7 ms during NSR versus 61.4±12.8 ms during cardiac memory; \(P<0.001\)).
To further define repolarization dispersion, we used an additional independent index of repolarization, the QRST integral. The QRST integral reflects only the gradient of repolarization by canceling the gradient of activation and has been shown to reflect changes in local APD. A negative QRST integral implies that the local APD is longer than in more distant (either transmural or lateral) regions, whereas a positive QRST integral indicates that local APD is shorter than in more distant regions. After RV pacing, the apical-lateral RV QRST integral became significantly more negative (10.4±1.6 mV·ms during NSR versus −12.4±2.8 mV·ms during cardiac memory; P<0.001), whereas the basal-lateral LV became significantly more positive (8.2±1.7 mV·ms during NSR versus −12.4±2.8 mV·ms during cardiac memory; P=0.001; Figure 5). These changes are consistent with action potential prolongation in the apical lateral RV relative to other regions.

**Repolarization Changes Present During RV Pacing**

To explore whether epicardial indices of repolarization exhibit changes during continued pacing, we compared measurements made at the onset of RV pacing, with measurements made during continued RV pacing after 1 month of continuous pacing. Surprisingly, no changes in ARI in the apical-lateral RV evolved over the course of 1 month of RV pacing (257.3±12.8 ms at the onset of pacing versus 264.6±9.7 ms at the end of pacing; P=1.34) (Figure 6A–6C). Whether this reflects a limited sensitivity of ARI to repolarization changes or a suppression of ARI prolongation because of continued pacing remains unclear (see Discussion section).

In contrast, the QRST integral exhibited a significant change from a positive to a negative value during the course of RV pacing from 14.2±2.5 mV·ms at the onset of RV pacing to −7.2±3.7 mV·ms at the end of RV pacing (P<0.001) (Figure 6D–6F), indicative of a local prolongation of APD relative to more distant regions. Given the lack of changes in epicardial ARI, this observation suggests that a repolarization gradient has developed either across the ventricular wall or involving the septum (neither of which can be directly observed using electrocardiographic imaging).

**Discussion**

This study used electrocardiographic imaging to determine the spatial pattern of activation and repolarization in the human heart during RV pacing-induced cardiac memory.
Our results provide novel insights into the pattern of pacing-induced electrical changes in vivo in the human heart. These results indicate that the body surface T-wave inversions of cardiac memory result from delayed repolarization of regions close to the site of ectopic pacing, reflecting action potential prolongation in this region and a resultant increase in both apical-basal and RV-LV gradients of repolarization. Interestingly, these changes are only partially evident during continuous RV pacing, as indicated by a QRST integral change without an associated change in the local ARI, whereas changes in both metrics of repolarization are evident in NSR after induction of cardiac memory.

**Spatial Gradients of Repolarization**

In principle, the body surface T-wave axis can be altered because of changes in apical-lateral, RV-LV, or transmural gradients of repolarization, and different experimental approaches have previously led to disparate conclusions regarding the altered repolarization gradient in cardiac memory. In the present study, we observed several spatial gradients of repolarization after induction of cardiac memory, including both RV-LV and apical-basal gradients of repolarization. In addition, the presence of a more negative QRST integral during continued RV pacing (indicative of a repolarization gradient) in the absence of changes in the epicardial repolarization time indirectly suggests a transmural gradient of repolarization. It thus seems that multiple spatial gradients underlie the T-wave inversions of cardiac memory.

**Spatial Pattern of Action Potential Prolongation**

The subjects in this study exhibited consistent patterns of repolarization underlying body surface T-wave inversions; all subjects had similar delayed repolarization due to ARI prolongation in the region of earliest pacemaker activation, despite different underlying pathological processes. This finding supports the original inference of Rosenbaum et al. that repolarization changes would be prominent in the region of earliest paced activation and contrasts with the findings of Jeyaraj et al. With regard to the contrasting results of Jeyaraj et al., we note that the canine study was performed using LV epicardial pacing rather than RV endocardial pacing; determining whether these disparate findings reflect the effects of different pacing sites or species-specific differences will require further study.

**Repolalization Changes During RV Pacing**

Although it seems intuitive that the molecular and cellular remodeling of cardiac memory are present during RV pacing (rather than appearing suddenly after the cessation of pacing), relatively little research has focused on identifying the manifestations of cardiac memory during RV pacing due to the secondary T-wave changes during pacing obscure the changes of cardiac memory. One study reports that the amplitude of the vectorcardiographic T wave is reduced during pacing, although the axis change is not evident until restoration of NSR. In addition, Rosenbaum et al. noted that the body surface QRST integral became more negative during continued RV pacing. The current findings shed further light on the repolarization changes present during pacing. In the cardiac regions destined to exhibit a prolonged ARI after cessation of pacing, the QRST integral becomes more negative during pacing and remains stable after cessation of pacing, indicating that at least some components of the repolarization gradient have evolved during pacing although the body surface T-wave manifestations remain partially masked.

In contrast, the epicardial ARI in this study exhibits the unpredicted behavior of remaining unchanged during continuous pacing and then becoming prolonged immediately upon cessation of pacing. Although the ARI is a well-validated albeit indirect measure of APD under a variety of conditions in animal models, it remains possible that during RV endocardial pacing in human subjects, it fails to accurately reflect local APD. Alternatively, it is possible that the epicardial ARI prolongation is suppressed during continued RV pacing. Intriguingly, Libbus et al. reported a similar observation in their study of pacing-induced changes in a canine transmural wedge preparation; epicardial APD shortened slightly during epicardial pacing but then became markedly prolonged after restoration of endocardial activation. Although not identical to the current study, this finding lends support to the hypothesis that continued pacing can suppress APD changes, which then become manifest after cessation of pacing. These observations contrast with a previous electrocardiographic imaging study of cardiac memory in which ARI prolongation was evident both before and after Wolff-Parkinson-White syndrome pathway ablation. The reason for this discrepancy remains unclear but may relate to the fact that in Wolff-Parkinson-White syndrome, the majority of the myocardium is activated through the normal conduction system, whereas in RV pacing most activation occurs through slower, direct myocyte connections.

**Mechanism of Cardiac Memory**

The molecular and cellular mechanism(s) underlying cardiac memory remain incompletely understood. In their original description of cardiac memory, Rosenbaum et al. speculated that altered electrotonic interactions due to the altered pattern of excitation gave rise to cardiac memory. This hypothesis gained experimental support from short-term experiments on canine wedge preparations. Interestingly, long-term cardiac memory in canine hearts has been shown to be associated with the downregulation of connexin 43 and a redistribution of gap junctions in epicardial cells, potentially altering local electrotonic interactions. It has also been suggested that the well-documented alterations in mechanical strain resulting from abnormal activation lead to cardiac memory via angiotensin II signaling. However, the most marked region of altered strain is located distant from the site of pacing, whereas most (but not all) studies indicate that the most marked electrical remodeling occurs close to the site of pacing. Conversely, regions close to the site of pacing exhibit reduced strain, perfusion, and oxygen uptake; whether these conditions contribute to local electrical remodeling remains unknown. The results reported here indicate that electrical remodeling is maximally close to the site of pacing and thus, indirectly, favor the hypotheses that...
either local electrotonic interactions or reduced mechanical strain underlie cardiac memory.

**Clinical Implications**

T-wave inversions occur in a variety of disease processes, including neurological injury, hypertrophic cardiomyopathy, and cardiac ischemia and infarction, in addition to cardiac memory; their prognostic significance depends on the causative pathology and on the uniformity of the underlying repolarization changes. It has been suggested that the abrupt repolarization changes that occur upon restoration of NSR after induction of cardiac memory may constitute an arrhythmogenic substrate, implying that frequent switching between pacing and NSR may be more unstable than maintaining pacing. The results of this study offer a potential mechanistic insight into these observations. Although some repolarization changes occur during continuous RV pacing (as evidenced by the altered QRST integral), epicardial APD changes can be suppressed by an altered activation pattern. Taken together, these results suggest the intriguing possibility that continuous pacing may be less arrhythmogenic than intermittent pacing. Further work is necessary to define whether there are clinically adverse outcomes as a consequence of intermittent RV pacing and, if so, to fully define the responsible mechanisms.

**Acknowledgments**

We thank Dr Pamela Woodard and Tim Street for expert assistance with computed tomography scans and Eric Novak for assistance with statistical analysis.

**Sources of Funding**

The present study was supported by National Institutes of Health (NIH) R01-HL-03343-26 and R01-HL-049054-18 grants (to Dr Rudy) and Washington University School of Medicine (Department of Internal Medicine) Mentors in Medicine grant (to Dr Marrus). Dr Marrus was also supported by NIH grant T32 HL-007275.

**Disclosures**

Dr Rudy cochairs the advisory board of and holds equity in CardioInsight Technologies. CardioInsight Technologies does not support any research conducted by Dr Rudy, including that presented here. Dr Rudy is the Fred Saigh Distinguished Professor at Washington University. The other authors have no conflicts to report.

**References**

Recent studies have drawn attention to the potentially deleterious effects of long-term right ventricular (RV) pacing on cardiac mechanical function. In addition, RV pacing is known to result in electrical changes (as manifested by an altered T-wave axis), a phenomenon described as cardiac memory, although a detailed understanding of the spatial pattern of repolarization changes resulting from RV pacing has remained lacking. Using noninvasive electrocardiographic imaging, the present study provides novel insights into the pattern of electrical remodeling induced by RV pacing. Two new insights emerged from the present study. First, the region close to the site of pacing exhibits a local action potential prolongation, resulting in a potentially arrhythmogenic dispersion of repolarization. Second, this dispersion of repolarization is only partially evident during continuous RV pacing, raising the intriguing possibility that the potentially arrhythmogenic substrate induced by RV pacing is only fully present after cessation of pacing. The clinical implications of these findings require further study, but the results offer mechanistic insights into the potential clinical sequelae of RV pacing.

Repolarization Changes Underlying Long-Term Cardiac Memory Due to Right Ventricular Pacing: Noninvasive Mapping With Electrocardiographic Imaging
Scott B. Marrus, Christopher M. Andrews, Daniel H. Cooper, Mitchell N. Faddis and Yoram Rudy

Circ Arrhythm Electrophysiol. 2012;5:773-781; originally published online July 6, 2012;
doi: 10.1161/CIRCEP.112.970491
Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3149. Online ISSN: 1941-3084

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circep.ahajournals.org/content/5/4/773

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Arrhythmia and Electrophysiology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Arrhythmia and Electrophysiology is online at:
http://circep.ahajournals.org//subscriptions/