Global Dynamic Coupling of Activation and Repolarization in the Human Ventricle

Arthur M. Yue, MRCP; Tim R. Betts, MD, MRCP; Paul R. Roberts, MD, MRCP; John M. Morgan, MD, FRCP

Background—The ability to determine spatial and dynamic changes in ventricular repolarization may help to understand arrhythmogenic mechanisms in humans. We hypothesized that noncontact mapping could be used to investigate global activation-repolarization coupling in the human ventricle during steady state and premature extrastimulation.

Methods and Results—Activation-recovery intervals (ARIs) determined from reconstructed unipolar electrograms by the Ensite system were analyzed during sinus rhythm, constant pacing, spontaneous ventricular ectopic beats, and premature stimulation at intermediate and short coupling intervals in the left or right ventricle of 13 patients (6 female; mean age, 48 years) without structural myocardial disease. ARIs were measured from 32 sites in each ventricle with the use of a method validated with monophasic action potential recordings and unipolar contact electrograms. Global T-wave distribution was displayed on a 3-dimensional geometry of the ventricle, with polarities opposite to the direction of activation during steady state and premature stimulation. There was a significant inverse correlation between activation times and ARIs during sinus rhythm, ventricular ectopy, and premature stimulation ($r=0.72$, slope $=-0.76$, $P<0.001$). Premature stimuli at short coupling intervals flattened the regression slope compared with sinus rhythm ($r=0.61$ versus $-0.81$; $P=0.05$), but the global pattern of repolarization was preserved. In comparison to our method, the Wyatt method of ARI measurement failed to demonstrate significant coupling between activation and repolarization ($r=0.34$, slope $=0.19$).

Conclusions—Global, dynamic repolarization mapping of the human ventricle is feasible. An inverse coupling of activation and repolarization during steady state and premature stimulation may preserve electric stability in the normal ventricle. (Circulation. 2005;112:2592-2601.)

Key Words: electrophysiology ■ mapping ■ repolarization ■ ventricles
patients presented with idiopathic monomorphic ventricular tachycardia, and 1 patient presented with ectopic atrial tachycardia (Table 1). They underwent initial evaluation with clinical history, physical examination, 12-lead ECG, and transthoracic echocardiography. Coronary angiography did not demonstrate clinically significant coronary artery disease, and left ventriculography was normal in all cases. MRI showed no structural abnormality of the right heart. All antiarrhythmic medications were discontinued for 5 half-life periods. The study was performed in the left or right ventricle in the postabsorptive state immediately after successful ablation of ventricular tachycardia or ectopic right atrial tachycardia. In the patient with right atrial tachycardia, right ventricular geometry was constructed after introducing the multielectrode array (MEA) catheter from atrium to ventricle after ablation. All patients had signed written consent before the study. Ethical approval of this study was granted by the Southampton and Southwest Hampshire research ethics committee.

**TABLE 1. Patient Characteristics**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Sex</th>
<th>Study Ventricle</th>
<th>Chamber Diameter, mm</th>
<th>Resting Sinus Rate, bpm</th>
<th>QTc Interval, ms</th>
<th>Cardiac Comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33</td>
<td>M</td>
<td>Left</td>
<td>46</td>
<td>53</td>
<td>380</td>
<td>Nil</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>F</td>
<td>Left</td>
<td>52</td>
<td>62</td>
<td>420</td>
<td>Nil</td>
</tr>
<tr>
<td>3</td>
<td>32</td>
<td>M</td>
<td>Left</td>
<td>34</td>
<td>70</td>
<td>402</td>
<td>Nil</td>
</tr>
<tr>
<td>4</td>
<td>74</td>
<td>M</td>
<td>Left</td>
<td>45</td>
<td>62</td>
<td>408</td>
<td>Mild CAD</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>F</td>
<td>Left</td>
<td>43</td>
<td>73</td>
<td>365</td>
<td>Nil</td>
</tr>
<tr>
<td>6</td>
<td>51</td>
<td>M</td>
<td>Left</td>
<td>38</td>
<td>66</td>
<td>388</td>
<td>Nil</td>
</tr>
<tr>
<td>7</td>
<td>61</td>
<td>M</td>
<td>Right</td>
<td>29</td>
<td>78</td>
<td>418</td>
<td>RBBB</td>
</tr>
<tr>
<td>8</td>
<td>55</td>
<td>F</td>
<td>Right</td>
<td>27</td>
<td>71</td>
<td>414</td>
<td>Nil</td>
</tr>
<tr>
<td>9</td>
<td>60</td>
<td>F</td>
<td>Right</td>
<td>27</td>
<td>74</td>
<td>402</td>
<td>Nil</td>
</tr>
<tr>
<td>10</td>
<td>69</td>
<td>M</td>
<td>Right</td>
<td>31</td>
<td>73</td>
<td>393</td>
<td>Nil</td>
</tr>
<tr>
<td>11</td>
<td>36</td>
<td>F</td>
<td>Right</td>
<td>25</td>
<td>76</td>
<td>417</td>
<td>Nil</td>
</tr>
<tr>
<td>12</td>
<td>43</td>
<td>F</td>
<td>Right</td>
<td>31</td>
<td>68</td>
<td>415</td>
<td>Small VSD</td>
</tr>
<tr>
<td>13</td>
<td>67</td>
<td>M</td>
<td>Right</td>
<td>30</td>
<td>66</td>
<td>394</td>
<td>Nil</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease; RBBB, right bundle branch block; and VSD, ventricular septal defect.

**Noncontact Mapping**

The technique of noncontact mapping with the use of the Ensite 3000 system (Endocardial Solutions Inc) has been described previously.10,11 The system consists of a 64-MEA mounted on a 7.5-ml inflatable balloon on a 9F catheter, an amplifier system, and a Silicon Graphics workstation. For left ventricular study, the MEA was introduced into the ventricle by the same route as the MEA catheter. The system calculated the position of the ablation catheter relative to the fixed, known position of the ring electrodes at either end of the MEA. By dragging the ablation catheter tip along the endocardial surface and constantly passing a 5-kHz locator signal to the 2 ring electrodes, a 3-dimensional geometry of the ventricle was determined. The intracavity signals were computed with the use of an inverse Laplace’s equation and projected onto the geometry. Data were stored on optical discs for offline analysis.

**Reconstructed Unipolar Electrograms**

Three different morphologies of unipolar electrogram T wave were defined: positive, negative, and biphasic. ARIs were measured by both the Wyatt method and an alternative method to investigate the implications of these 2 approaches on the estimation of global repolarization in a normal ventricle. In the Wyatt method, local ARI was measured between times of dV/dtmax of the QRS and the dV/dtmin of the T wave in the unipolar electrogram of all T-wave morphologies. In the alternative method, recovery was determined at the dV/dtmin of the T wave for negative T wave, at the dV/dtmax of the T wave for positive T wave, and at the mean time between dV/dtmax and dV/dtmin for biphasic T wave (Figure 1). Unipolar electrograms with ST-segment elevation without discernible T-wave upstroke were rarely observed in cases in which the pacing electrode was in contact with ventricular endocardium and were excluded from measurement with the Wyatt method. For a T wave with double peak derivatives, recovery time was taken at the mean between 2 peaks. Activation time (AT) was defined as the interval from the onset of QRS or pacing stimulus from surface ECG to the onset of ARI. Repolarization time (RT) was taken as the sum of local activation time and ARI.

**Premature Stimulation**

Constant right ventricular pacing (S1) with a bipolar woven catheter (Bard EP Inc) at the right ventricular apex was performed for 2 minutes at cycle lengths of 400 ms with a pulse width of 2-ms duration and stimulus strength of twice diastolic threshold. After steady state has been established, an extrastimulus (S2) was introduced at every 10-beat cycle. A “short” S1-S2 coupling interval was defined as the shortest interval that resulted in S2 capture. An “intermediate” S1-S2 coupling interval was defined as 75% of total S1-S2 shortening from steady state to S2 refractoriness.

**Contact Unipolar Recordings**

In 2 patients (12 and 13), reconstructed T-wave morphologies were validated with contact unipolar electrogram recordings at multiple endocardial sites. Contact unipolar electrograms were measured between the tip of the ablation catheter and the most proximal reference electrode (20 cm from the tip) of the MEA catheter by jump connections in the breakout box. Thus, the same reference electrode was used for determining contact and reconstructed unipolar electrograms by the Ensite system. The EnGuide locator signal was directed through the ablation catheter tip to display its location on the geometry. A total of 117 recordings at 39 different ventricular sites were made (3 consecutive beats analyzed from each site) during sinus rhythm, spontaneous ventricular ectopy, and right ventricular apical pacing.
Data Analysis

Data were analyzed with the Silicon Graphics workstation with the use of the standard Precision software (version 4.0). Measurements were made manually from electrograms displayed on a Silicon Graphics color monitor at 200 mm/s resolution. The use of electronic calipers from the workstation allows timings of activation and repolarization to be determined to an accuracy of 1 ms.

Validation of T-Wave Morphology

Three consecutive paired recordings were selected from each site for comparison, including abrupt changes in local T-wave morphology caused by ventricular ectopic beats or pacing (Figure 2). Recording bandwidth was set at 0.1 to 300 Hz for contact and unipolar electrogram recordings. Simultaneous voltage data from contact and unipolar electrogram T waves were exported for cross-correlation analysis. Differences in timing between unipolar electrograms and contact electrograms were measured. The distance of each sampling site of the geometry from the center of the MEA was documented with the use of the workstation algorithm.

Measurement of Global ARIs

A custom-designed template was used to display the unipolar electrogram and its first derivative (dV/dt) from 2 endocardial sites at a time. A total of 32 sites were analyzed from each ventricle, with 2 sites 1 cm apart from each of 16 predefined segments in the left or right ventricular geometry (Figure 3). Samples were evenly selected from the entire ventricle on the basis of anatomic grounds and not on electrogram appearances. For timing measurement of the first derivatives of the QRS and T waves, filter bandwidth was selected at 0.1 to 25 Hz. Global dispersion of RT was calculated by the range of RTs within a map (maximum RT−minimum RT). Adjacent dispersion of RT was defined as the difference between 2 adjacent sites (1 cm apart) within each segment of the ventricle. Sinus rhythm, ventricular ectopy, and pacing recordings were randomly selected for analysis.

T-Wave Maps

Endocardial T-wave distribution was displayed as colors on the geometry by using the isochronal map algorithm, with detection sensitivity set at maximum and the filter bandwidth set at 0.1 to 300 Hz. After the “static map” option was selected, calipers were placed from the onset to the end of a T wave on the surface ECG. Because the algorithm determined local timings from the peak dV/dtmin of the selected waveforms, sites with negative and biphasic unipolar electrogram T waves, which had earlier peak dV/dtmin, could be separated from sites with positive T waves, which had much later peak dV/dtmin. Accordingly, areas with negative and biphasic T waves were displayed in yellow to red and positive T waves in blue on the isochronal map. Therefore, the spatial distribution of different T-wave morphologies for any selected beat could be displayed on the geometry.

Statistical Analysis

Continuous data that were approximately normally distributed were presented as mean±SD. T-wave morphologies for paired unipolar
electrograms and contact electrograms were compared by cross-correlation analysis.\textsuperscript{10} The correlation between activation time and ARI or RT for each map was calculated with the use of Pearson’s correlation coefficient test and simple linear regression analysis. Continuous data that were not approximately normally distributed were compared with the Wilcoxon matched pair signed rank test. Median regression slopes during sinus rhythm and premature stimulation were compared with the Wilcoxon matched pair signed rank test paired by patient and state. Thirty-two sites from each ventricle were analyzed to detect a correlation coefficient of 0.60 with 90% power. A probability value of $<0.05$ was considered statistically significant.

**Results**

**Validation of T-Wave Morphology**

A total of 117 recordings of paired contact and reconstructed electrograms were compared. The overall mean correlation of T-wave morphology was $0.97 \pm 0.06$, with a difference in timing between unipolar electrograms and contact electrograms of $4 \pm 14$ ms. Correlation was statistically significant for all 3 T-wave morphologies. Cross-correlation coefficients were 0.98 ($P<0.001$) for negative T wave, 0.96 ($P<0.001$) for positive T wave, and 0.96 ($P<0.001$) for biphasic T wave. The mean distance of sampling sites from the center of the MEA was $24 \pm 5$ mm.

**Endocardial T-Wave Distribution**

A total of 54 ventricular maps were constructed from 13 patients, of which there were 13 from sinus rhythm, 12 from ventricular ectopy, 12 from constant ventricular pacing, 8 during intermediate premature stimuli, and 9 during short premature stimuli. In 45 of 54 maps, T-wave morphologies were arranged in a spatially predictable manner, with positive T waves located in areas of earliest endocardial activation, negative T waves in regions of latest activation, and biphasic T waves in between. The global pattern of T-wave distribution was consistent during sinus rhythm (Figure 4), spontaneous ventricular ectopic beats (Figure 5), constant pacing, and extrastimulation (Figure 6). Repolarization distribution was preserved in the global ventricle, and changes in T-wave morphology at short premature coupling intervals only occurred within border regions of T-wave transition (Figure 6).

In the 9 maps with atypical distributions, 4 maps showed only positive T waves, 2 maps showed only negative T waves, and 3 maps showed no relationship between T-wave morphology and activation times.

**Global Activation-Repolarization Coupling**

Of the 1728 measurements of ARIs made from 54 maps during steady states and extrastimuli, 43 (2\%) were excluded from analysis because of flat or complex T waves, and an additional 21 (1\%) were specifically excluded from Wyatt method measurement because of ST elevations in which the upstroke of T wave could not be defined.

With the use of our alternative method for ARI determination in both ventricles, ARIs were found to correlate inversely and linearly with ATs during sinus rhythm, ventricular ectopic beats, constant right ventricular pacing at 400-ms drive cycle lengths, and premature stimulation (Figure 7). The inverse coupling between activation and repolarization could be demonstrated even in maps with uniform or atypical T-wave distribution. The overall correlation was 0.72, with a regression slope of $-0.76$ ($P<0.001$) (Table 2). The mean intermediate S1-S2 coupling interval during premature stimulation was $260 \pm 17$ ms, and mean short S1-S2 interval was $204 \pm 22$ ms. During intermediate and short premature stimulations, not only was the inverse activation-relationship maintained, but there was also a significant trend toward progressive flattening of regression slope with short premature extrastimuli compared with sinus rhythm ($-0.61$ versus $-0.81$; $P=0.05$) (Figure 8).

**Dispersion of Total Repolarization Times**

Global dispersion of repolarization during steady state was $45$ ms in sinus rhythm and $49$ ms during constant ventricular pacing. Similar values were found for ventricular ectopic beats ($43$ ms) and premature stimulation at intermediate coupling intervals ($47$ ms), but global dispersion was increased by premature stimulation at short coupling intervals to $50$ ms (Table 2). Adjacent dispersion of repolarization was small and was not altered by premature stimulation with an overall mean of $6 \pm 3$ ms.
Comparison of Wyatt Method With Alternative Method

If ARIs were measured with the Wyatt method for the global ventricle, the activation-repolarization relationship was not statistically significant ($r=0.34$, 52% of slopes with $P<0.05$) in comparison to the inverse correlation with the use of the alternative method ($r=0.72$, 91% of slopes with $P<0.001$) during steady state and premature stimulation (Table 3). The use of the Wyatt method was also associated with greater global dispersion of repolarization times compared with the alternative method (99 versus 47 ms; $P<0.001$) because of differences in repolarization times in regions with positive T waves (Figure 7).

Discussion

The close correlation of reconstructed unipolar T-wave morphology with contact electrograms in this report, combined with the excellent correlation between reconstructed ARIs and monophasic action potential durations,$^6$ demonstrates that noncontact mapping is a valid technique for quantifying ventricular repolarization and endocardial T-wave distribution in humans.

Global Distribution of T-Wave Polarities

Unipolar T-wave polarities are opposite to the deflection resulting from the direction of activation,$^12$ hence, the positive T waves are in areas of earliest activation, and negative T waves are at sites of latest activation. This finding has been shown previously during steady states in the dog heart with the use of transmural electrodes,$^{13,14}$ in the swine endocardium with the use of sequential contact recordings,$^4$ and in the human epicardium with the use of contact electrodes.$^9$ We have demonstrated these repolarization gradients in the human endocardium not only in steady state but also after premature stimulation. A transmural gradient may also exist during sinus rhythm, with T waves being positive in the epicardium and negative in the endocardium in the canine heart.$^{14}$ These transventricular and transmural potential gradients are used to predict the directionality of ventricular repolarization from areas with positive to negative potentials. Because our technique is validated with endocardial contact recordings, T-wave distribution maps could be used to analyze instantaneous spatial forces of repolarization in the human ventricle.

Inverse Coupling of Activation and Repolarization

The data presented in this study suggest that activation is inversely coupled to repolarization in the normal ventricle, so
that areas activated the earliest are associated with longer local action potential durations than areas activated the latest. Our findings concord with recent reports of global repolarization mapping in the swine and human ventricles.3–5 Franz et al.3 demonstrated such an inverse relationship using monophasic action potential recordings in the human ventricle during sinus rhythm and further showed that the epicardium activated later but repolarized earlier than the endocardium, which accounted for the T-wave concordance of the normal ECG. Gepstein et al.4 constructed high-density repolarization maps of the swine left ventricle using electroanatomic mapping. They found that during both sinus rhythm and right ventricular pacing, ARIs were the longest near the area of earliest activation and gradually shortened with increasing distance from this site. Yuan et al.5 also found an inverse linear relationship between local activation times and monophasic action potential durations in one patient during ventricular ectopic beats and another patient during ventricular tachycardia.

Electrotonic interaction is a potential mechanism that may relate activation to repolarization sequence over the global ventricle. Gap junction proteins may mediate the transfer of action potential between adjacent myocytes15 over extended distances.16 Activation wave fronts from ectopic or paced rhythms, which preferentially utilize intermyocyte conduction rather than specialized conduction systems, may particularly be influenced by this phenomenon. As a result of electrotonic interaction, transverse or longitudinal excitation propagation along the long axis of ventricular fibers determines the spatial gradient of ventricular repolarization.17 However, when nonuniform activation is simulated by introducing anisotropic conductivities, marked spatial dispersion of repolarization is induced.18 There is also evidence to suggest that repolarization currents applied during repolarization may shorten the local action potential.3,12 Therefore, an upstream cell that repolarizes earlier than a downstream cell may, through electrotonic interaction, shorten the action potential duration of the downstream cell. If this pattern were uniformly maintained over the entire ventricle, an inverse linear relationship between activation and repolarization times could be formed.

**Global Dispersion of Repolarization**

It is debated whether repolarization in the regions with latest activation completes before or after areas of earliest activation, as reflected by the slope of linear regression for action potential duration against activation time. Were the mean regression slope to be more negative than −1, as demon-
strated by Franz et al\textsuperscript{3} at 5 to 11 recording sites, then repolarization would complete earliest in regions of latest activation. If the regression slope were more positive than $-1$, as shown in our study ($-0.76$) or others that also employed 3-dimensional mapping technologies,\textsuperscript{4,5} the converse would be true. In either case, activation is correlated inversely with repolarization, which may be a mechanism whereby spatial dispersion of repolarization is minimized in the normal ventricle. A progressive and homogeneous reduction of local ARI with increasing distance and activation delay from the site of earliest activation may minimize the overall dyssynchrony of ventricular repolarization times. Thus, the median global dispersion of repolarization times during steady state and premature stimulation in our patients

Figure 6. Isochronal maps of the right ventricle during constant pacing and after a premature extrastimulus in patient 7 (anterior posterior view). An isochronal activation map during constant right ventricular apical pacing is shown (A). T-wave maps are shown during constant pacing (B) and premature stimulus (C) (positive T waves in blue; negative and biphasic T waves in yellow to red). Virtual electrogram 3 is selected at the border region to demonstrate a change in T-wave morphology from biphasic to positive after a premature stimulus (arrow). However, the global pattern of T-wave distribution is preserved, with positive T waves located at sites of earliest activation and negative T waves located at sites of latest activation. RVOT indicates right ventricular outflow tract; RVA, right ventricular apex; and TV, tricuspid valve.
ranges from 43 to 50 ms, which is consistent with values obtained from prior studies in human subjects without structural or repolarization abnormalities that range from 30 to 60 ms. Spatial dispersion of ventricular repolarization of a much greater magnitude ranging from 90 to 190 ms is frequently required for the induction of ventricular arrhythmias under clinical conditions.

Spatial dispersion of ventricular repolarization of a much greater magnitude ranging from 90 to 190 ms is frequently required for the induction of ventricular arrhythmias under clinical conditions.

**TABLE 2. Activation-Repolarization Relationship During Steady State and Premature Stimulation (Alternative Method)**

<table>
<thead>
<tr>
<th>Maps</th>
<th>AT/ARI Slope</th>
<th>AT/ARI Correlation (r)</th>
<th>RT Dispersion, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus rhythm</td>
<td>13</td>
<td>-0.81</td>
<td>0.74</td>
</tr>
<tr>
<td>Ventricular ectopy</td>
<td>12</td>
<td>-0.76</td>
<td>0.76</td>
</tr>
<tr>
<td>Constant pacing</td>
<td>12</td>
<td>-0.70</td>
<td>0.71</td>
</tr>
<tr>
<td>Premature stimulation (intermediate)</td>
<td>8</td>
<td>-0.77</td>
<td>0.69</td>
</tr>
<tr>
<td>Premature stimulation (short)</td>
<td>9</td>
<td>-0.61*</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Median values are presented. *P=0.05 compared with sinus rhythm.

**Figure 7.** A, Relationship between AT and ARI. A typical example is taken from patient 7 during constant ventricular pacing. A significant inverse correlation is demonstrated with the alternative method (closed circles; slope=−1.03, r=0.92, P<0.001) but not the Wyatt method (open triangles; slope=0.27, r=0.28, P=0.06). B, Relationship between AT and total RT. RTs estimated by the alternative method (closed circles) are constant over the global endocardium (range, 34 ms). RTs measured by the Wyatt method (open triangles) are heterogeneous at short AT (range, 76 ms).

**Figure 8.** ARI regression slopes during steady state, ventricular ectopy, and premature stimulation for all patients (box and whisker plot shows median, interquartile range, and extreme values). SR indicates sinus rhythm; VE, ventricular ectopy; Pace, constant right ventricular pacing; and R1 and R2, premature stimuli at intermediate and short coupling intervals, respectively. *P=0.05.

**Coupling of Activation and Repolarization During Premature Stimulation**

We have shown that the global pattern of T-wave distribution and activation-repolarization coupling gradient are both preserved during premature stimulation and that this effect is instantaneous, occurring after a single extrastimulus or ventricular ectopic beat. This inverse coupling appears to maintain uniformity of spatial and temporal repolarization patterns and electric stability in the normal heart during both steady state and spontaneous ectopic activity. Extrastimuli at progressive proximity to the preceding beat might induce ventricular arrhythmias by flattening the regression slope and increasing global dispersion of repolarization. However, we have not observed any reversal of the action potential gradients and T-wave morphologies at short coupling intervals, as demonstrated by optical mapping studies on the guinea pig epicardium. We note in our patients that changes in T-wave morphology sometimes occur during short premature stimulation but are limited to small border regions, with the overall global distribution maintained. Therefore, it is possible that the disparity is related to optical mapping data being sampled from a relatively small area or the difference between epicardial and endocardial response to extrastimulation.

Activation-repolarization coupling during single ectopic beats or premature stimulation in our patients without structural heart disease probably represents a "primary" effect of depolarization modulating its own repolarization gradient. As such, there is no prior electric remodeling, and the polarities of T wave remain opposite to the direction of activation. However, there is a trend toward a lesser negative regression slope during premature stimulation compared with sinus rhythm, which may suggest an instantaneous adaptation effect. If abnormal activation were to persist, electric remod-
el ing could be induced and manifested after return to sinus rhythm as “secondary” abnormal repolarization pattern and loss of normal activation-repolarization coupling.24,25

Methodology of Determining Repolarization From Unipolar Electrograms

The Wyatt approach for determining ARIs is based on theoretical derivation26 and has undergone systematic validation.8,27 However, a number of studies have reported that the Wyatt method may underestimate ARIs of the positive T-wave polarity,4,6,9 and the error may be more pronounced during premature stimulation. Our study shows that by using the Wyatt method, the relationship between activation and repolarization is altered with loss of linearity, inverse correlation, and statistical significance. Furthermore, global dispersion of repolarization is greater when measured by the Wyatt method compared with the alternative method. It is our opinion that this is an overestimation of dispersion of repolarization, but the implications of the differences between the 2 methods require further evaluation.

Clinical Implications

Dispersion of refractoriness has been shown in experimental studies to favor the development of reentry ventricular arrhythmias,2,28,29 but its role in humans is not yet established. We have shown that it is feasible to quantify T-wave distribution and global activation-repolarization coupling during steady state and premature stimulation. A tight inverse coupling between activation and repolarization in the global heart could protect the normal heart from developing ventricular arrhythmias in the presence of extrastimulation at short coupling intervals. On the contrary, disturbances of this coupling by structural heart disease or disorders of ion channels may be intensely arrhythmogenic. Our technique can be used to investigate arrhythmic mechanisms and identify risk markers for patients with these disease processes. The ability of noncontact mapping to display high-density global distribution of T waves could also be valuable in future studies of cardiac memory or electric remodeling.

Limitations

Although T-wave mapping provides a visual representation of T-wave distribution in a 3-dimensional geometry, the color scales do not reflect local repolarization timings. However, an algorithm can be developed on the basis of the aforementioned criteria to generate isochronal maps of global repolarization times. For practical and ethical reasons, our study has been conducted in one ventricle per patient, and therefore true transventricular repolarization gradients could not be measured directly. Our measurement methods and data are comparable with previous studies in which contact catheter techniques were used, but in the absence of a gold standard for measuring global and instantaneous ventricular repolarization, our data do not disprove the validity of the Wyatt approach.

Conclusions

It is feasible to use noncontact mapping to study global repolarization dynamics in the human ventricle. In the normal heart, this technique has advanced the understanding that during premature stimulation, activation and repolarization are tightly coupled to preserve electric homogeneity.

Acknowledgments

This study was supported by research funding from Endocardial Solutions, St Jude Medical, and the Wessex Cardiac Electrophysiology Research Fund to Dr Yue.

Disclosure

Drs Yue and Betts have previously participated in scientific studies for Endocardial Solutions.

References


Global Dynamic Coupling of Activation and Repolarization in the Human Ventricle

Arthur M. Yue, MRCP; Tim R. Betts, MD, MRCP; Paul R. Roberts, MD, MRCP; John M. Morgan, MD, FRCP

Background—The ability to determine spatial and dynamic changes in ventricular repolarization may help to understand arrhythmogenic mechanisms in humans. We hypothesized that noncontact mapping could be used to investigate global activation-repolarization coupling in the human ventricle during steady state and premature extrastimulation.

Methods and Results—Activation-recovery intervals (ARIs) determined from reconstructed unipolar electrograms by the Ensite system were analyzed during sinus rhythm, constant pacing, spontaneous ventricular ectopic beats, and premature stimulation at intermediate and short coupling intervals in the left or right ventricle of 13 patients (6 female; mean age, 48 years) without structural myocardial disease. ARIs were measured from 32 sites in each ventricle with the use of a method validated with monophasic action potential recordings and unipolar contact electrograms. Global T-wave distribution was displayed on a 3-dimensional geometry of the ventricle, with polarities opposite to the direction of activation during steady state and premature stimulation. There was a significant inverse correlation between activation times and ARIs during sinus rhythm, ventricular ectopy, and premature stimulation ($r=-0.72$, slope $=-0.76$, $P<0.001$). Premature stimuli at short coupling intervals flattened the regression slope compared with sinus rhythm ($r=-0.61$ versus $r=-0.81$; $P=0.05$), but the global pattern of repolarization was preserved. In comparison to our method, the Wyatt method of ARI measurement failed to demonstrate significant coupling between activation and repolarization ($r=0.34$, slope $=0.19$).

Conclusions—Global, dynamic repolarization mapping of the human ventricle is feasible. An inverse coupling of activation and repolarization during steady state and premature stimulation may preserve electric stability in the normal ventricle. (Circulation. 2005;112:2592-2601.)

Key Words: electrophysiology ▪ mapping ▪ repolarization ▪ ventricles

The activation-repolarization relationship is crucial in determining ventricular arrhythmogenic mechanisms. Disturbances in the dynamic interplay between activation and repolarization patterns have been linked to the induction and maintenance of ventricular arrhythmias in experimental models of coronary artery disease and the long QT syndrome. Conversely, an inverse coupling between activation and repolarization could maintain ventricular electric stability during steady states. However, studies in humans have been limited by the lack of a robust clinical technique to measure instantaneously global changes in cardiac repolarization.

Noncontact mapping can assess global repolarization changes in the human ventricle instantaneously. We have validated the use of activation-recovery intervals (ARIs) reconstructed by noncontact mapping with endocardial monophasic action potential recordings in humans. However, T-wave morphologies from reconstructed unipolar electrograms were not specifically validated with contact recordings, and the feasibility of our method to analyze high-density global repolarization data and T-wave distribution on the entire ventricle was not demonstrated. The Wyatt method determines ARI by estimating recovery at the maximum derivative of the T wave, but it has been shown to underestimate ARIs with positive T-wave polarities. The use of this approach to estimate global activation-repolarization coupling has not been previously examined.

In this study we investigated the activation-repolarization coupling and endocardial T-wave distribution in the normal ventricle during steady state, spontaneous ventricular ectopic beats, and premature stimuli at intermediate and short coupling intervals using a noncontact mapping method we have developed. In addition, we compared this approach with the Wyatt method to examine the activation-repolarization relationship in the human ventricle.

Methods

Patients

Thirteen patients (6 female; mean age, 48 years) who underwent radiofrequency ablation treatment for ventricular or atrial tachycardias guided by noncontact mapping in the Wessex Cardiac Center, Southampton, UK, were enrolled into the study. Twelve
patients presented with idiopathic monomorphic ventricular tachycardia, and 1 patient presented with ectopic atrial tachycardia (Table 1). They underwent initial evaluation with clinical history, physical examination, 12-lead ECG, and transthoracic echocardiography. Coronary angiography did not demonstrate clinically significant coronary artery disease, and left ventriculography was normal in all cases. MRI showed no structural abnormality of the right heart. All antiarrhythmic medications were discontinued for 5 half-life periods. The study was performed in the left or right ventricle in the postabsorptive state immediately after successful ablation of ventricular tachycardia or ectopic right atrial tachycardia. In the patient with right atrial tachycardia, right ventricular geometry was constructed after introducing the multielectrode array (MEA) catheter from atrium to ventricle after ablation. All patients had signed written consent before the study. Ethical approval of this study was granted by the Southampton and Southwest Hampshire research ethics committee.

Noncontact Mapping

The technique of noncontact mapping with the use of the Ensite 3000 system (Endocardial Solutions Inc) has been described previously.10,11 The system consists of a 64-MEA mounted on a 7.5-ml, inflatable balloon on a 9F catheter, an amplifier system, and a Silicon Graphics workstation. For left ventricular study, the MEA was introduced under fluoroscopic guidance from the left femoral artery via the retrograde transaortic route into the ventricle. For right ventricular study, the MEA was introduced from the left femoral to ventricle after ablation. All patients had signed written consent before the study. Ethical approval of this study was granted by the Southampton and Southwest Hampshire research ethics committee.

TABLE 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Sex</th>
<th>Study Ventricle</th>
<th>Chamber Diameter, mm</th>
<th>Resting Sinus Rate, bpm</th>
<th>QTc</th>
<th>Cardiac Comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33</td>
<td>M</td>
<td>Left</td>
<td>46</td>
<td>53</td>
<td>380</td>
<td>Nil</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>F</td>
<td>Left</td>
<td>52</td>
<td>62</td>
<td>420</td>
<td>Nil</td>
</tr>
<tr>
<td>3</td>
<td>32</td>
<td>M</td>
<td>Left</td>
<td>34</td>
<td>70</td>
<td>402</td>
<td>Nil</td>
</tr>
<tr>
<td>4</td>
<td>74</td>
<td>M</td>
<td>Left</td>
<td>45</td>
<td>62</td>
<td>408</td>
<td>Mild CAD</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>F</td>
<td>Left</td>
<td>43</td>
<td>73</td>
<td>365</td>
<td>Nil</td>
</tr>
<tr>
<td>6</td>
<td>51</td>
<td>M</td>
<td>Left</td>
<td>38</td>
<td>66</td>
<td>388</td>
<td>Nil</td>
</tr>
<tr>
<td>7</td>
<td>61</td>
<td>M</td>
<td>Right</td>
<td>29</td>
<td>78</td>
<td>418</td>
<td>RBBB</td>
</tr>
<tr>
<td>8</td>
<td>55</td>
<td>F</td>
<td>Right</td>
<td>27</td>
<td>71</td>
<td>414</td>
<td>Nil</td>
</tr>
<tr>
<td>9</td>
<td>60</td>
<td>F</td>
<td>Right</td>
<td>27</td>
<td>74</td>
<td>402</td>
<td>Nil</td>
</tr>
<tr>
<td>10</td>
<td>69</td>
<td>M</td>
<td>Right</td>
<td>31</td>
<td>73</td>
<td>393</td>
<td>Nil</td>
</tr>
<tr>
<td>11</td>
<td>36</td>
<td>F</td>
<td>Right</td>
<td>25</td>
<td>76</td>
<td>417</td>
<td>Nil</td>
</tr>
<tr>
<td>12</td>
<td>43</td>
<td>F</td>
<td>Right</td>
<td>31</td>
<td>68</td>
<td>415</td>
<td>Small VSD</td>
</tr>
<tr>
<td>13</td>
<td>67</td>
<td>M</td>
<td>Right</td>
<td>30</td>
<td>66</td>
<td>394</td>
<td>Nil</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease; RBBB, right bundle branch block; and VSD, ventricular septal defect.

Premature Stimulation

Constant right ventricular pacing (S1) with a bipolar woven catheter (Bard EP Inc) at the right ventricular apex was performed for 2 minutes at cycle lengths of 400 ms with a pulse width of 2-ms duration and stimulus strength of twice diastolic threshold. After steady state has been established, an extrastimulus (S2) was introduced at every 10-beat cycle. A “short” S1-S2 coupling interval was defined as the shortest interval that resulted in S2 capture. An “intermediate” S1-S2 coupling interval was defined as 75% of total S1-S2 shortening from steady state to S2 refractoriness.

Contact Unipolar Recordings

In 2 patients (12 and 13), reconstructed T-wave morphologies were validated with contact unipolar electrogram recordings at multiple endocardial sites. Contact unipolar electrograms were measured between the tip of the ablation catheter and the most proximal reference electrode (20 cm from the tip) of the MEA catheter by jump connections in the breakout box. Thus, the same reference electrode was used for determining contact and reconstructed unipolar electrograms by the Ensite system. The EnGuide locator signal was directed through the ablation catheter tip to display its location on the geometry. A total of 117 recordings at 39 different ventricular sites were made (3 consecutive beats analyzed from each site) during sinus rhythm, spontaneous ventricular ectopy, and right ventricular apical pacing.

Reconstructed Unipolar Electrograms

Three different morphologies of unipolar electrogram T wave were defined: positive, negative, and biphasic. ARIs were measured by both the Wyatt method and an alternative method to investigate the implications of these 2 approaches on the estimation of global repolarization in a normal ventricle. In the Wyatt method, local ARI was measured between times of dV/dtmin of the QRS and the dV/dtmax of the T wave in the unipolar electrogram of all T-wave morphologies.8 In the alternative method, recovery was determined at the dV/dtmax of the T wave for positive T wave, at the dV/dtmin of the T wave for positive T wave, and at the mean time between dV/dtmax and dV/dtmin for biphasic T wave (Figure 1). Unipolar electrograms with ST-segment elevation without discernible T-wave upstroke were rarely observed in cases in which the pacing electrode was in contact with ventricular endocardium and were excluded from measurement with the Wyatt method. For a T wave with double peak derivatives, recovery time was taken at the mean between 2 peaks. Activation time (AT) was defined as the interval from the onset of QRS or pacing stimulus from surface ECG to the onset of ARI. Repolarization time (RT) was taken as the sum of local activation time and ARI.
Data Analysis

Data were analyzed with the Silicon Graphics workstation with the use of the standard Precision software (version 4.0). Measurements were made manually from electrograms displayed on a Silicon Graphics color monitor at 200 mm/s resolution. The use of electronic calipers from the workstation allows timings of activation and repolarization to be determined to an accuracy of 1 ms.

Validation of T-Wave Morphology

Three consecutive paired recordings were selected from each site for comparison, including abrupt changes in local T-wave morphology caused by ventricular ectopic beats or pacing (Figure 2). Recording bandwidth was set at 0.1 to 300 Hz for contact and unipolar electrogram recordings. Simultaneous voltage data from contact and unipolar electrogram T waves were exported for cross-correlation analysis. Differences in timing between unipolar electrograms and contact electrograms were measured. The distance of each sampling site of the geometry from the center of the MEA was documented with the use of the workstation algorithm.

Measurement of Global ARIs

A custom-designed template was used to display the unipolar electrogram and its first derivative (dV/dt) from 2 endocardial sites at a time. A total of 32 sites were analyzed from each ventricle, with 2 sites 1 cm apart from each of 16 predefined segments in the left or right ventricular geometry (Figure 3). Samples were evenly selected from the entire ventricle on the basis of anatomic grounds and not on electrogram appearances. For timing measurement of the first derivatives of the QRS and T waves, filter bandwidth was selected at 0.1 to 25 Hz. Global dispersion of RT was calculated by the range of RTs within a map (maximum RT−minimum RT). Adjacent dispersion of RT was defined as the difference between 2 adjacent sites (1 cm apart) within each segment of the ventricle. Sinus rhythm, ventricular ectopy, and pacing recordings were randomly selected for analysis.

T-Wave Maps

Endocardial T-wave distribution was displayed as colors on the geometry by using the isochronal map algorithm, with detection sensitivity set at maximum and the filter bandwidth set at 0.1 to 300 Hz. After the “static map” option was selected, calipers were placed from the onset to the end of a T wave on the surface ECG. Because the algorithm determined local timings from the peak dV/dt\textsubscript{min} of the selected waveforms, sites with negative and biphasic unipolar electrogram T waves, which had earlier peak dV/dt\textsubscript{min}, could be separated from sites with positive T waves, which had much later peak dV/dt\textsubscript{min}. Accordingly, areas with negative and biphasic T waves were displayed in yellow to red and positive T waves in blue on the isochronal map. Therefore, the spatial distribution of different T-wave morphologies for any selected beat could be displayed on the geometry.

Statistical Analysis

Continuous data that were approximately normally distributed were presented as mean±SD. T-wave morphologies for paired unipolar
electrograms and contact electrograms were compared by cross-correlation analysis. The correlation between activation time and ARI or RT for each map was calculated with the use of Pearson’s correlation coefficient test and simple linear regression analysis. Continuous data that were not approximately normally distributed were compared with the Wilcoxon matched pair signed rank test. Median regression slopes during sinus rhythm and premature stimulation were compared with the Wilcoxon matched pair signed rank test paired by patient and state. Thirty-two sites from each ventricle were analyzed to detect a correlation coefficient of 0.60 with 90% power. A probability value of <0.05 was considered statistically significant.

Results
Validation of T-Wave Morphology
A total of 117 recordings of paired contact and reconstructed electrograms were compared. The overall mean correlation of T-wave morphology was 0.97 ± 0.06, with a difference in timing between unipolar electrograms and contact electrograms of 4 ± 14 ms. Correlation was statistically significant for all 3 T-wave morphologies. Cross-correlation coefficients were 0.98 (P < 0.001) for negative T wave, 0.96 (P < 0.001) for positive T wave, and 0.96 (P < 0.001) for biphasic T wave. The mean distance of sampling sites from the center of the MEA was 24 ± 5 mm.

Endocardial T-Wave Distribution
A total of 54 ventricular maps were constructed from 13 patients, of which there were 13 from sinus rhythm, 12 from ventricular ectopy, 12 from constant ventricular pacing, 8 during intermediate premature stimuli, and 9 during short premature stimuli. In 45 of 54 maps, T-wave morphologies were arranged in a spatially predictable manner, with positive T waves located in areas of earliest endocardial activation, negative T waves in regions of latest activation, and biphasic T waves in between. The global pattern of T-wave distribution was consistent during sinus rhythm (Figure 4), spontaneous ventricular ectopic beats (Figure 5), constant pacing, and extrastimulation (Figure 6). Repolarization distribution was preserved in the global ventricle, and changes in T-wave morphology at short premature coupling intervals only occurred within border regions of T-wave transition (Figure 6).

Global Activation-Repolarization Coupling
Of the 1728 measurements of ARIs made from 54 maps during steady states and extrastimuli, 43 (2%) were excluded from analysis because of flat or complex T waves, and an additional 21 (1%) were specifically excluded from Wyatt method measurement because of ST elevations in which the upstroke of T wave could not be defined.

With the use of our alternative method for ARI determination in both ventricles, ARIs were found to correlate inversely and linearly with ATs during sinus rhythm, ventricular ectopic beats, constant right ventricular pacing at 400-ms drive cycle lengths, and premature stimulation (Figure 7). The inverse coupling between activation and repolarization could be demonstrated even in maps with uniform or atypical T-wave distribution. The overall correlation was 0.72, with a regression slope of −0.76 (P < 0.001) (Table 2). The mean intermediate S1-S2 coupling interval during premature stimulation was 260 ± 17 ms, and mean short S1-S2 interval was 204 ± 22 ms. During intermediate and short premature stimulations, not only was the inverse activation-relationship maintained, but there was also a significant trend toward progressive flattening of regression slope with short premature extrastimuli compared with sinus rhythm (−0.61 versus −0.81; P = 0.05) (Figure 8).

Dispersion of Total Repolarization Times
Global dispersion of repolarization during steady state was 45 ms in sinus rhythm and 49 ms during constant ventricular pacing. Similar values were found for ventricular ectopic beats (43 ms) and premature stimulation at intermediate coupling intervals (47 ms), but global dispersion was increased by premature stimulation at short coupling intervals to 50 ms (Table 2). Adjacent dispersion of repolarization was small and was not altered by premature stimulation with an overall mean of 6 ± 3 ms.
Comparison of Wyatt Method With Alternative Method

If ARIs were measured with the Wyatt method for the global ventricle, the activation-repolarization relationship was not statistically significant ($r=0.34$, 52% of slopes with $P<0.05$) in comparison to the inverse correlation with the use of the alternative method ($r=0.72$, 91% of slopes with $P<0.001$) during steady state and premature stimulation (Table 3). The use of the Wyatt method was also associated with greater global dispersion of repolarization times compared with the alternative method (99 versus 47 ms; $P<0.001$) because of differences in repolarization times in regions with positive T waves (Figure 7).

Discussion

The close correlation of reconstructed unipolar T-wave morphology with contact electrograms in this report, combined with the excellent correlation between reconstructed ARIs and monophasic action potential durations, demonstrates that noncontact mapping is a valid technique for quantifying ventricular repolarization and endocardial T-wave distribution in humans.

Global Distribution of T-Wave Polarities

Unipolar T-wave polarities are opposite to the deflection resulting from the direction of activation; hence, the positive T waves are in areas of earliest activation, and negative T waves are at sites of latest activation. This finding has been shown previously during steady states in the dog heart with the use of transmural electrodes, in the swine endocardium with the use of sequential contact recordings, and in the human epicardium with the use of contact electrodes. We have demonstrated these repolarization gradients in the human endocardium not only in steady state but also after premature stimulation. A transmural gradient may also exist during sinus rhythm, with T waves being positive in the epicardium and negative in the endocardium in the canine heart. These transventricular and transmural potential gradients are used to predict the directionality of ventricular repolarization from areas with positive to negative potentials. Because our technique is validated with endocardial contact recordings, T-wave distribution maps could be used to analyze instantaneous spatial forces of repolarization in the human ventricle.

Inverse Coupling of Activation and Repolarization

The data presented in this study suggest that activation is inversely coupled to repolarization in the normal ventricle, so

Figure 4. Isochronal maps of the left ventricle during sinus rhythm in patient 1 (left anterior oblique view). Activation map (A) and T wave map (B) during repolarization (positive T waves in blue; negative and biphasic T waves in yellow to red) are shown. Positive T waves are located at sites of earliest activation, and negative T waves are located at sites of latest activation. Ant indicates anterior; Lat, lateral.
that areas activated the earliest are associated with longer local action potential durations than areas activated the latest. Our findings concur with recent reports of global repolarization mapping in the swine and human ventricles.3–5 Franz et al3 demonstrated such an inverse relationship using monophasic action potential recordings in the human ventricle during sinus rhythm and further showed that the epicardium activated later but repolarized earlier than the endocardium, which accounted for the T-wave concordance of the normal ECG. Gepstein et al4 constructed high-density repolarization maps of the swine left ventricle using electroanatomic mapping. They found that during both sinus rhythm and right ventricular pacing, ARIs were the longest near the area of earliest activation and gradually shortened with increasing distance from this site. Yuan et al5 also found an inverse linear relationship between local activation times and monophasic action potential durations in one patient during ventricular ectopic beats and another patient during ventricular tachycardia.

Electrotonic interaction is a potential mechanism that may relate activation to repolarization sequence over the global ventricle. Gap junction proteins may mediate the transfer of action potential between adjacent myocytes over extended distances.16 Activation wave fronts from ectopic or paced rhythms, which preferentially utilize intermyocyte conduction rather than specialized conduction systems, may particularly be influenced by this phenomenon. As a result of electrotonic interaction, transverse or longitudinal excitation propagation along the long axis of ventricular fibers determines the spatial gradient of ventricular repolarization.17 However, when nonuniform activation is simulated by introducing anisotropic conductivities, marked spatial dispersion of repolarization is induced.18 There is also evidence to suggest that repolarization currents applied during repolarization may shorten the local action potential.13,12 Therefore, an upstream cell that repolarizes earlier than a downstream cell may, through electrotonic interaction, shorten the action potential duration of the downstream cell. If this pattern were uniformly maintained over the entire ventricle, an inverse linear relationship between activation and repolarization times could be formed.

**Global Dispersion of Repolarization**

It is debated whether repolarization in the regions with latest activation completes before or after areas of earliest activation, as reflected by the slope of linear regression for action potential duration against activation time. Were the mean regression slope to be more negative than −1, as demon-

---

**Figure 5.** Isochronal maps of the left ventricle during spontaneous ventricular ectopic activity in patient 1 (anterior-posterior view). Activation map (A) and T wave map during repolarization (B) (positive T waves in blue; negative and biphasic T waves in yellow to red) are shown. Positive T waves are located at sites of earliest activation, and negative T waves are located at sites of latest activation. Ant indicates anterior; AV, aortic valve.
strated by Franz et al\textsuperscript{3} at 5 to 11 recording sites, then repolarization would complete earliest in regions of latest activation. If the regression slope were more positive than $-1$, as shown in our study ($-0.76$) or others that also employed 3-dimensional mapping technologies,\textsuperscript{4,5} the converse would be true. In either case, activation is correlated inversely with repolarization, which may be a mechanism whereby spatial dispersion of repolarization is minimized in the normal ventricle. A progressive and homogeneous reduction of local ARI with increasing distance and activation delay from the site of earliest activation may minimize the overall dyssynchrony of ventricular repolarization times.

Figure 6. Isochronal maps of the right ventricle during constant pacing and after a premature extrastimulus in patient 7 (anterior posterior view). An isochronal activation map during constant right ventricular apical pacing is shown (A). T-wave maps are shown during constant pacing (B) and premature stimulus (C) (positive T waves in blue; negative and biphasic T waves in yellow to red). Virtual electrogram 3 is selected at the border region to demonstrate a change in T-wave morphology from biphasic to positive after a premature stimulus (arrow). However, the global pattern of T-wave distribution is preserved, with positive T waves located at sites of earliest activation and negative T waves located at sites of latest activation. RVOT indicates right ventricular outflow tract; RVA, right ventricular apex; and TV, tricuspid valve.
Thus, the median global dispersion of repolarization times during steady state and premature stimulation in our patients ranges from 43 to 50 ms, which is consistent with values obtained from prior studies in human subjects without structural or repolarization abnormalities that range from 30 to 60 ms.3,19–21

Spatial dispersion of ventricular repolarization of a much greater magnitude ranging from 90 to 190 ms is frequently required for the induction of ventricular arrhythmias under clinical conditions.21,22

**Coupling of Activation and Repolarization During Premature Stimulation**

We have shown that the global pattern of T-wave distribution and activation-repolarization coupling gradient are both preserved during premature stimulation and that this effect is instantaneous, occurring after a single extrastimulus or ventricular ectopic beat. This inverse coupling appears to maintain uniformity of spatial and temporal repolarization patterns and electric stability in the normal heart during both steady state and spontaneous ectopic activity. Extrastimuli at progressive proximity to the preceding beat might induce ventricular arrhythmias by flattening the regression slope and increasing global dispersion of repolarization. However, we have not observed any reversal of the action potential gradients and T-wave morphologies at short coupling intervals, as demonstrated by optical mapping studies on the guinea pig epicardium.23 We note in our patients that changes in T-wave morphology sometimes occur during short premature stimulation but are limited to small border regions, with the overall global distribution maintained. Therefore, it is possible that the disparity is related to optical mapping data being sampled from a relatively small area or the difference between epicardial and endocardial response to extrastimulation.

Activation-repolarization coupling during single ectopic beats or premature stimulation in our patients without structural heart disease probably represents a “primary” effect of depolarization modulating its own repolarization gradient.24 As such, there is no prior electric remodeling, and the polarities of T wave remain opposite to the direction of activation. However, there is a trend toward a lesser negative

---

**TABLE 2. Activation-Repolarization Relationship During Steady State and Premature Stimulation (Alternative Method)**

<table>
<thead>
<tr>
<th>Maps</th>
<th>AT/AR Slope</th>
<th>AT/AR Correlation (r)</th>
<th>RT Dispersion, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus rhythm</td>
<td>13</td>
<td>−0.81</td>
<td>0.74</td>
</tr>
<tr>
<td>Ventricular ectopy</td>
<td>12</td>
<td>−0.76</td>
<td>0.76</td>
</tr>
<tr>
<td>Constant pacing</td>
<td>12</td>
<td>−0.70</td>
<td>0.71</td>
</tr>
<tr>
<td>Premature stimulation (intermediate)</td>
<td>8</td>
<td>−0.77</td>
<td>0.69</td>
</tr>
<tr>
<td>Premature stimulation (short)</td>
<td>9</td>
<td>−0.61*</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Median values are presented.

*P=0.05 compared with sinus rhythm.
regression slope during premature stimulation compared with sinus rhythm, which may suggest an instantaneous adaptation effect. If abnormal activation were to persist, electric remodeling could be induced and manifested after return to sinus rhythm as “secondary” abnormal repolarization pattern and loss of normal activation-repolarization coupling.\textsuperscript{24,25}

**Methodology of Determining Repolarization From Unipolar Electrograms**

The Wyatt approach for determining ARIs is based on theoretical derivation\textsuperscript{26} and has undergone systematic validation.\textsuperscript{8,27} However, a number of studies have reported that the Wyatt method may underestimate ARIs of the positive T-wave polarity,\textsuperscript{4,6,9} and the error may be more pronounced during premature stimulation. Our study shows that by using the Wyatt method, the relationship between activation and repolarization is altered with loss of linearity, inverse correlation, and statistical significance. Furthermore, global dispersion of repolarization is greater when measured by the Wyatt method compared with the alternative method. It is our opinion that this is an overestimation of dispersion of repolarization, but the implications of the differences between the 2 methods require further evaluation.

**Clinical Implications**

Dispersion of refractoriness has been shown in experimental studies to favor the development of reentry ventricular arrhythmias,\textsuperscript{2,28,29} but its role in humans is not yet established. We have shown that it is feasible to quantify T-wave distribution and global activation-repolarization coupling during steady state and premature stimulation. A tight inverse coupling between activation and repolarization in the global heart could protect the normal heart from developing ventricular arrhythmias in the presence of extrastimulation at short coupling intervals. On the contrary, disturbances of this coupling by structural heart disease or disorders of ion channels may be intensely arrhythmogenic. Our technique can be used to investigate arrhythmic mechanisms and identify risk markers for patients with these disease processes. The ability of noncontact mapping to display high-density global distribution of T waves could also be valuable in future studies of cardiac memory or electric remodeling.

**Limitations**

Although T-wave mapping provides a visual representation of T-wave distribution in a 3-dimensional geometry, the color scales do not reflect local repolarization timings. However, an algorithm can be developed on the basis of the aforementioned criteria to generate isochronal maps of global repolarization times. For practical and ethical reasons, our study has been conducted in one ventricle per patient, and therefore true transventricular repolarization gradients could not be measured directly. Our measurement methods and data are comparable with previous studies in which contact catheter techniques were used, but in the absence of a gold standard for measuring global and instantaneous ventricular repolarization, our data do not disprove the validity of the Wyatt approach.

**Conclusions**

It is feasible to use noncontact mapping to study global repolarization dynamics in the human ventricle. In the normal heart, this technique has advanced the understanding that during premature stimulation, activation and repolarization are tightly coupled to preserve electric homogeneity.

**Acknowledgments**

This study was supported by research funding from Endocardial Solutions, St Jude Medical, and the Wessex Cardiac Electrophysiology Research Fund to Dr Yue.

**Disclosure**

Drs Yue and Betts have previously participated in scientific studies for Endocardial Solutions.

**References**

9. Chen PS, Moser KM, Dembisky WP, Auger WR, Daily PO, Calisi CM, Jamieson SW, Feld GK. Epicardial activation and repolarization patterns

**TABLE 3. Comparison Between Wyatt and Alternative Methods**

<table>
<thead>
<tr>
<th></th>
<th>Wyatt method</th>
<th>Alternative method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maps</td>
<td>54</td>
<td>54</td>
</tr>
<tr>
<td>Regression Slope</td>
<td>0.19</td>
<td>-0.76*</td>
</tr>
<tr>
<td>AT/ARI Correlation</td>
<td>0.34</td>
<td>0.72*</td>
</tr>
<tr>
<td>AT/ARI</td>
<td>52%</td>
<td>98%</td>
</tr>
<tr>
<td>P&lt;0.05</td>
<td>26%</td>
<td>91%</td>
</tr>
<tr>
<td>P&lt;0.001</td>
<td>99</td>
<td>47*</td>
</tr>
</tbody>
</table>

Median values are presented. *P<0.001 compared with Wyatt method.


