Left Ventricular Epicardial Electrograms Show Divergent Changes in Action Potential Duration in Responders and Nonresponders to Cardiac Resynchronization Therapy

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Background—A consistent feature of electrophysiological remodeling in heart failure is ventricular action potential duration (APD) prolongation. However, the effect of reverse remodeling on APD during cardiac resynchronization therapy (CRT) has not been determined in these patients. We hypothesized (1) that CRT may alter APD and (2) that the effect of CRT on APD may be different in patients who exhibit a good hemodynamic response to CRT compared with those with a poor response.

Methods and Results—Left ventricular (LV) activation recovery intervals, as a surrogate for APD, were measured from the LV epicardium in 13 patients at day 0, 6 weeks, and 6 months after CRT implant. Responders to CRT were defined as those demonstrating a ≥15% reduction in LV end-systolic volume at 6 months. The responder group had a significant reduction in LV activation recovery interval (mean, −13±12 ms; median, −16 ms; interquartile range, −2 to −19 ms) during right ventricular pacing at 6 months (P<0.05). Conversely, the nonresponders showed a significant increase in activation recovery interval (mean, +22 ms±16; median, 17 ms; interquartile range, 8 to 35 ms; P<0.05). One patient in each group was on amiodarone.

Conclusions—In patients with heart failure, LV epicardial APD (activation recovery interval) altered during CRT. The effect on APD was opposite in patients showing a good hemodynamic response compared with nonresponders. The findings may provide an explanation for the persistent high incidence of arrhythmias in some patients with CRT and the additional mortality benefit observed in responders of CRT. (Circ Arrhythm Electrophysiol. 2013;6:265-271.)

Key Words: action potential duration ■ activation recovery interval ■ cardiac remodeling ■ cardiac resynchronization therapy ■ mechano-electric feedback

A consistent feature of electrophysiological remodeling in heart failure is ventricular action potential duration (APD) prolongation.1 The effect of cardiac resynchronization therapy (CRT) and reverse remodeling on APD duration has not been determined in these patients.

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CRT in patients with heart failure has been shown to be beneficial in terms of symptomatic improvement and overall mortality. Recently, the MultiCenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) trial, the Resynchronization Reverse Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) trial, and the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT) have demonstrated that CRT provided an incremental overall survival benefit to implantable cardioverter defibrillator therapy alone in heart failure patients.2-4 However, earlier studies showed that the incidence of arrhythmia and sudden death continues to be high despite CRT inferring the possible need for additional protection from implantable cardioverter defibrillator.5,6 These observations highlighted a need to further elucidate the effect of CRT on electrophysiology.

CRT is associated with anatomic and electric remodeling, and evidence suggests these two processes are linked.7-9 The effect of CRT on APD has been studied in a canine heart failure model, which showed APD shortening in cells from the lateral left ventricular (LV) wall.10 However, evidence suggests that the electrophysiological effects of CRT may vary according to the anatomic and hemodynamic profiles,11-14 underlining the need to obtain information directly from the hearts of patients with heart failure.
We hypothesized that APD may be modified during CRT, and the effect on APD may vary in patients who exhibit a beneficial response to CRT compared with those with a poor response. To assess this, we set out to record activation recovery intervals (ARI) as a surrogate measure of APD from the LV epicardial lead of a CRT device at intervals during the first 6 months after implantation. ARI has been theoretically and experimentally validated as a reliable surrogate marker of regional APD. It has advantages compared with other measures of repolarization, including enabling analysis of regional electric properties, unlike the QT interval, which is a more global measurement. It also avoids the need for long pacing protocols required for effective refractory period and the pro-arrhythmic risk of premature stimulation required to measure effective refractory period.

Methods

Study Population and Protocol

The study was approved by the local institution ethics committee, and all patients gave written informed consent to participate. Thirteen patients who fulfilled the standard criteria for CRT were prospectively recruited to the study before their device implant. The selection criteria included drug refractory symptomatic heart failure with New York Heart Association (NYHA) class II to IV, impaired LV ejection fraction (LVEF) ≤35% with a QRS duration ≥120 ms. The baseline patient characteristics are shown in Table 1. Clinical status according to NYHA class and Minnesota heart failure questionnaires and echocardiographic measures of LV function were assessed at baseline (day 0) and 6 months after device implant. Transthoracic echocardiography was performed using a GE Vivid 7 scanner (General Electric-Vingmed, Milwaukee, WI) at baseline and 6 months after implant to acquire standard 2-dimensional images of LV dimensions and EF during breath-hold in standard apical 2- and 4-chamber views. LVEF and dimensions were measured using the 2-dimensional modified biplane Simpson’s method. Analysis was done on EchoPac 6.0.1 (General Electric- Vingmed).

All 13 patients were implanted with the Quartet Model 1458Q LV pacing lead (St. Jude Medical, St. Paul, MN) via the coronary sinus in conjunction with a Unity Quadra CD 3251-40Q generator (St. Jude Medical). The atrial–ventricular and ventricular–ventricular delays were empirically set at 120 ms and LV 30 ms ahead of right ventricular (RV) at implant. CRT device optimization was performed at 6 weeks after implant per our institute’s standard clinical care protocol. At this time, the atrial–ventricular and ventricular–ventricular delays were adjusted under echocardiographic guidance using mitral valve inflow Doppler signals and aortic valve outflow velocity–time intervals to achieve the best hemodynamic benefit. There were no changes in the LV pacing vectors and output stimulus strength in the patients over the 6-month period. The LV pacing output strength was 2.0 V at 0.5 ms pulse width for all patients.

At day 0 after implant, a 30-s recording of the LV unipolar electrocardiogram (UEG) signal was made via the device programmer (Merlin Patient Care System, Model 3650, St. Jude Medical) during DDD-RV or VVI-RV pacing, depending on whether the patient was in sinus rhythm or in atrial fibrillation. This enabled comparisons between patients with sinus rhythm and those with atrial fibrillation at identical heart rate to eliminate the influence of heart rate on ARI. This study protocol is also clinically relevant in that during CRT, in addition to LV pacing, the RV is also paced, which would change the regional ARI when the patient is in intrinsic ventricular rhythm. To eliminate the influence of variable heart rate on ARI, UEG recordings were made after at least 2 minutes of pacing at a constant rate of 10 beats above the patient’s intrinsic heart rate. The same recordings were repeated 6 weeks and 6 months after implant at the same heart rate. The 30-s LV UEG recordings were analyzed offline using a software script developed by our group within the MATLAB environment (MathWorks, Natick, MA) to derive the ARI. ARIs were measured using conventional validated criteria from dv/dt min of the QRS of the UEG to dv/dt max of the local T wave. An example showing the measurement and the stability of recordings is illustrated in Figure 1. Responders to CRT were defined as those demonstrating a ≥215% reduction in LV end-systolic volume at 6 months. The echocardiography assessor was blinded to the ARI results.

Statistical Analysis

Data were expressed by the mean±SD or median and interquartile range. Continuous variables were compared using the t test where data distribution met the criteria for normality; otherwise, the Wilcoxon rank test or Mann–Whitney U test was used for dependent or independent observation, respectively. Categorical variables were compared using the χ² test. A P value of <0.05 was considered to be statistically significant. All statistics were performed using computer software SPSS Statistics, version 20 (IBM SPSS, New York, NY). Additional post hoc power analysis based on the collected data assuming nonparametric distribution was performed using G*Power, version 3.1.5 (Kiel, Germany).

Results

All 13 patients underwent successful CRT implant. The epicardial LV leads were targeted in the lateral and posterior walls in all subjects. The positions of the LV lead tip where UEG recordings were made are illustrated in Figure 2.
was no significant difference between the positions of the RV lead between the responder and nonresponders.

Although 4 of 6 patients in the nonresponder group, compared with 3 of 7 patients in the responder group, had LV lead tip positioned in the apical region, the use of quadripolar leads allowed pacing sites away from the apex in some cases to maximize clinical benefit for the patient and avoid phrenic nerve stimulation. The mean absolute distance between the LV lead tip which ARI was measured to the LV pacing cathode was 10±13 mm in the responder group and 11±19 mm in the nonresponder group. (Note that these measures are derived from the absolute distance between the vectors along the quadripolar leads, and absolute accuracy is limited because of the oblique course of epicardial vein and the position and shape of lead sitting within the vein.) During the 6 months of CRT, all the patients (responders and nonresponders) were paced via bipolar vectors (LV and RV). The pacing vectors and pacing outputs were not changed during the 6-month study duration. The percentages of the biventricular pacing were the same between the 2 groups. There were no major differences between the optimized A–V delays and V–V delays between the responder and nonresponders in the study cohort. A–V delays were 127±10 ms and 123±5 ms in the patients with sinus rhythm in the responders and nonresponder groups, respectively. Four of 7 patients in the responder group had V–V delays of 0 ms, the other 3 patients had LV ahead of RV by 30 ms. Three of 6 patients in the nonresponder group had V–V delays of 0 ms, 1 of 6 patients had LV ahead by 20 ms, and the other 2 had LV ahead by 30 ms.

On the basis of the LV end-systolic volume reduction ≥15% at 6 months after implant, 7 patients (54%) were considered to be echocardiographic responders. The mean change in LV end-systolic volume at 6 months after CRT device implant was −36±15% in the responder group and +3±5% in the nonresponder group compared with baseline (P<0.001). The mean LVEF at 6 months was 39±7% in the responder group and 31±5% in the nonresponder group (P=0.045). The mean NYHA class improved by 1.5±0.9 class in the responder group and remained unchanged in the nonresponder group. Minnesota heart failure questionnaire score at 6 months was 31±23 in both groups. The clinical and echocardiographic indices at 6 months after CRT are shown in Table 2.

LV UEGs were recorded during DDD-RV or VVI-RV pacing at a fixed heart rate ranged from 80 bpm to 120 beats per minute within the cohort (the same heart rates were maintained during recordings at day 0, 6 weeks, and 6 months for individual patients). The LV ARI during RV pacing at day 0, 6 weeks, and 6 months are summarized in Table 3.

The paired changes in LVAR during RV pacing at day 0 among the responders and nonresponders are shown in Figure 3. At 6 months, the responders showed a significant decrease in ARI (P=0.043), whereas conversely the nonresponders showed a significant increase in ARI (P=0.046). These divergent effects were evident by 6 weeks, although not reaching significance for the responders. Mean, median values, and confidence intervals for the data are shown in Table 3.

In Figure 4, changes in LVARI at 6 months compared with day 0 among the responders and nonresponders are plotted against changes in LVEF response to CRT. The changes between the LV ARI and the changes in LV function were not linear. In the responders, the LV ARI during RV pacing decreased with an improvement in LV function; however, the LVARI increased in the nonresponders despite insignificant changes in LV function.

Post hoc power calculation showed that the study had a 95% power to detect a change in LVARI at 6 months after CRT between responders and nonresponders at the 0.05 significance level.

Discussion

We have shown, for the first time, that LV APD (ARI) changes during CRT with APD shortening in responders and lengthening or remaining the same in nonresponders to CRT. These changes seem to be coupled with positive reverse remodeling in the CRT responders. This supports the hypothesis that electric remodeling accompanies the hemodynamic remodeling associated with CRT in heart failure patients with dyssynchrony.

Figure 1. An example of left ventricular unipolar electrogram raw data recording demonstrating activation recovery interval (ARI).
Comparison With Previous Studies

Our results are in keeping with the observed APD shortening in the LV lateral wall after 3 weeks of resynchronization therapy in a canine dyssynchrony heart failure model. Recent human studies using ECG QT and T-wave measurements have shown evidence suggestive of remodeling of APD associated with CRT in heart failure patients with dyssynchrony. Wecke et al. demonstrated an increase in repolarization changes, measured by T-wave vectors and T-peak to T-end intervals, in the first 2 weeks of initiating CRT therapy treatment in heart failure patients with left bundle-branch block. In a group of established responders of CRT, Braunischweig et al. demonstrated a transient initial increase followed by a sustained reduction of QT and JT interval after reinitiation of resynchronization therapy. Perhaps more comparable with the results of our study, Lellouche et al. observed a reduction in QT intervals in responders to CRT, which was associated with a lower incidence of appropriate implantable cardioverter defibrillator therapies. Our results also lend support to the in silico modeling of the adaptive effects of mechano-electric coupling relationship in the dyssynchronous heart by Kuijpers et al.

Mechanisms for APD Changes

APDs are lengthened in the myocytes of the failing heart. The mechanisms underlying APD changes in heart failure and APD changes during CRT are at present unclear. A fairly consistent finding is a downregulation of repolarizing K+ currents together with changes in depolarizing Na+ and Ca2+ currents and calcium cycling. Studies of animal models of heart failure have demonstrated that considerable heterogeneity exists in these changes.

Dyssynchronous heart failure, as in the present patient cohort, is associated with regional variation in myocardial strain patterns, with low strain occurring in early activated anteroseptal regions and high strain in late activated lateral posterior LV walls. In heart failure patients with left bundle-branch block, the lateral wall is usually the latest area of activation. This discordant contraction between the early and late activated segments increases the strain and workload of the late activated regions. As a result, there is an increase in the LV preload, further stretching the myocardium leading to long-term structural modeling. However, mechanical dyssynchrony can also occur in the absence of intraventricular electric delays. An animal study has demonstrated that simple changes in LV afterload by clamping the aorta can acutely induce dyssynchrony in the presence of normal ventricular electric delays, suggesting a close mechano-electric coupling involved in the LV activation. Studies with canine dyssynchrony heart failure models have demonstrated APD shortening in the early activated low strain regions and APD prolongation in the late activated regions of high strain. These observations suggest that the myocardium can respond to changes in stretch by altering its electric properties through a process of mechano-electric feedback. This mechanism may be a trigger for the changes in APD seen with dyssynchronous heart failure and with its reversal through CRT. Jeyaraj et al. have suggested that this trigger may be mediated through intermediates, including stretch-activated nonselective ion channels, cytoskeletal proteins, and stretch-activated signal transduction pathways.

However, the observation that sarcolemmal ion channels and even individual potassium channels seem to be differentially regulated in models of heart failure suggests that multiple mechanisms may be involved. CRT results in partial reversal of the electrophysiological consequences of heart failure, including the downregulation of repolarizing K+ currents. This would be consistent with the shortening of APD at the lateral LV wall that we observed at 6 weeks and 6 months after the initiation of CRT in the responders. Our results are also in line with the APD shortening observed in an animal dyssynchrony heart failure model by Aiba et al.

The mechanisms of reverse electric remodeling during CRT have yet to be fully elucidated. Several mechanisms have been proposed, including reversal of the abnormal activation pattern, reversal of abnormal regional strain patterns, and a role for improved β-adrenergic function. Considerable overlap is likely to exist between these multiple mechanisms that underlie remodeling and reverse remodeling. For example, mechano-electric feedback and changes in electrotonic current load...
caused by altered activation sequence are a component of myocardial memory. It is possible, therefore, that the memory function may play a role in our results. Varied coupling between these mechanisms in responders and nonresponders may, in part, explain the nonlinear relationship between the differential changes in action potential we observed in the responders and nonresponders. It is worth noting there were a greater proportion of patients with ischemic cardiomyopathy in the nonresponder group. The regional scars may hinder both mechano- and electric remodeling to CRT in patients with previous myocardial infarction. During device implant, LV leads were positioned outside scarred myocardium on the basis of electric sensing parameters and prior knowledge of scar location identified from cardiac MRI. Our study is underpowered to assess the influence of the ischemic pathogenesis on the changes in LV ARI. However, it would be of interest for future studies to combine with cardiac MRI with scar geometry and examine the possible influence of scar on reverse remodeling.

Significance of APD Changes, Impact on Arrhythmogenesis

The effect of CRT on arrhythmogenesis remains controversial. It has been suggested on the basis of clinical and experimental evidence that CRT incorporating LV epicardial pacing may promote rather than reverse electric remodeling and be potentially proarrhythmic. APD changes in heart failure are characteristically heterogeneous resulting in increased dispersion of repolarization, which is potentially proarrhythmic. Biventricular pacing incorporating an LV epicardial lead reverses the normal activation sequence across the lateral LV wall. This has been shown in canine wedge preparations to result in increased dispersion of transmural repolarization across the LV wall and be proarrhythmic. Others have further demonstrated that in the canine dyssynchrony heart failure model, the transregional dispersion of APD occurs to a greater extent than the transmural dispersion of APD in response to dyssynchrony. In a recent clinical study, increased dispersion of repolarization measured by interlead difference in T-peak to T-end intervals was associated with a higher incidence of implantable cardioverter defibrillator therapies in patients with CRT.

Reversal of APD lengthening by CRT has been shown experimentally to reduce dispersion and hence be potentially arrhythmia protective. Interpreting our results in this context must remain speculative, as we have no evidence that APD at

Table 3. Epicardial LV ARI During Steady Rate RV Pacing at Day 0, 6 Weeks, and 6 Months of CRT

<table>
<thead>
<tr>
<th>LV ARI</th>
<th>ms</th>
<th>Responders</th>
<th>Nonresponders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0</td>
<td>Mean 259±53</td>
<td>253±25</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median 238; IQR, 213 to 303</td>
<td>262; IQR, 224 to 270</td>
<td></td>
</tr>
<tr>
<td>Week 6</td>
<td>Mean 255±50</td>
<td>-4±18*</td>
<td>265±25</td>
</tr>
<tr>
<td></td>
<td>Median 252; IQR, 224 to 287</td>
<td>0; IQR, -20 to -11*</td>
<td></td>
</tr>
<tr>
<td>Month 6</td>
<td>Mean 246±47</td>
<td>-13±12‡</td>
<td>272±22</td>
</tr>
<tr>
<td></td>
<td>Median 235; IQR, 215 to 287</td>
<td>-16; IQR, -19 to -2‡</td>
<td></td>
</tr>
</tbody>
</table>

Δ denotes changes compared with day 0. Data are expressed as mean±SD and median and interquartile range (IQR). ARI indicates activation recovery intervals; CRT, cardiac resynchronization therapy; and LV, left ventricular.

*Δ at 6wk.
†P<0.05 compared with day 0.
‡Δ at 6 mo.
the lateral LV wall at the site of our recordings was actually prolonged as a result of heart failure. However, because it is well known that APD prolongation at the lateral LV wall is a consistent finding in heart failure, we would suggest that APD shortening at this site in the responders would generate a more favorable antiarrhythmia substrate profile. Conversely the APD lengthening that we observed in the nonresponders would create a less favorable arrhythmia substrate. The observation that APD prolongs in nonresponders despite insignificant changes in LV function and dimension suggests in the absence of positive reverse functional and structural remodeling, LV epicardial pacing may potentially be proarrhythmic.12,13 This would be in keeping with clinical observations suggesting a reduced arrhythmic risk in responders to CRT.7,44 and an increased arrhythmic risk in nonresponders.39 It is possible that the additional electric remodeling that accompanies the structural and functional remodeling observed in responders of CRT outweighs the initial proarrhythmic increase in repolarization dispersion caused by LV epicardial and biventricular pacing.23

Limitations
Our study was limited, but was large enough to demonstrate significant result at 95% power. Due to a limitation of the device programmer, we were only able to record UEGs from distal pole of the quadripolar lead; improved spatial mapping could be of interest for future studies. Although we did not have a measure of regional wall stress or strain in our study, previous studies have demonstrated CRT results in a more synchronous LV strain patterns in responders compared with nonresponders.45,46 Further study is needed to explore the regional strain pattern in the accompanying regions where we measured LV ARI to elucidate whether mechanical stretch or strain may be the trigger for our observed changes in APD. It has been shown that increased dispersion of repolarization measured from body surface ECG leads varied between responders and nonresponders. The ARI measured only reflected regional electric activity at the site of the distal LV lead. It would be of interest to see how this regional change is related to the global LV repolarization time and dispersion. A much larger patient cohort with longer follow-up period is needed to achieve this and relate to the arrhythmic outcomes in these patients.

Conclusion
In patients with dyssynchronous heart failure, LV epicardial APD measured by ARI altered during CRT. The effect on APD was opposite in patients showing a positive echocardiographic remodeling response compared with nonresponders. The findings may provide an explanation to the persistent high incidence of arrhythmias in some patients with CRT and the additional mortality benefit observed in responders of CRT.

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Disclosures
None.

References
17. Haws CW, Lux RL. Correlation between *in vivo* transmembrane action potential durations and activation-recovery intervals from electrograms.


**CLINICAL PERSPECTIVE**

Heart failure is associated with mechanical and electrophysiological remodeling. A consistent feature of importance in arrhythmogenesis is ventricular action potential duration (APD) prolongation. Cardiac resynchronization therapy (CRT) is associated with anatomic and electric reverse remodeling. However, the effect of reverse remodeling on APD during CRT has not been determined. Using activation recovery intervals (ARI) as a surrogate measure of APD from the left ventricular epicardial lead of a CRT device at intervals during the first 6 months after implantation, we found that in patients with dysynchronous heart failure, left ventricular APD changed during CRT. APD shortened in responders with clinical improvement and lengthened or remained the same in nonresponders to CRT. This supports the hypothesis that electric remodeling accompanies the reverse remodeling associated with CRT in heart failure patients with dys synchrony. The effect on APD was the opposite in patients showing a positive echocardiographic remodeling response compared with nonresponders. These findings may provide an explanation for the persistent high incidence of arrhythmias in some patients with CRT and the additional mortality benefit observed in responders of CRT.
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