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

Zhong Chen, MBBS, MRCP*; Ben Hanson, PhD*; Manav Sohal, MBBS, MRCP; Eva Sammut, MBBS, MRCP; Nick Child, MBBS, MRCP; Anoop Shetty, MD, MRCP; Ryan Boucher, BSc; Julian Bostock, BSc; Jaswinder Gill, MD, FRCP; Gerald Carr-White, PhD, FRCP; C. Aldo Rinaldi, MD, FRCP; Peter Taggart, MD, DSc, FRCP

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.

Clinical Perspective on p 271

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.

Received September 6, 2012; accepted February 14, 2013.

From the Kings College London, London, United kingdom (Z.C., M.S., E.S., N.C., A.S., J.B., J.G., G.C.-W., C.A.R.); University College London, London, United Kingdom (B.H., P.T.); and St. Jude Medical, Stratford Upon Avon, United Kingdom (R.B.).

*Z. Chen and Dr Hanson contributed equally to this article.

Correspondence to Zhong Chen, MBBS, MRCP, Department of Imaging Science and Biomedical Engineering, The Rayne Institute, Kings's College London, 4th Floor Lambeth Wing, St. Thomas' Hospital Campus, London SE1 7EH, United Kingdom. E-mail zhong.chen@kcl.ac.uk

Circ Arrhythm Electrophysiol **is available at http://circep.ahajournals.org** **DOI: 10.1161/CIRCEP.112.000148**

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.[15–19] 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 proarrhythmic 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.

Table 1. Baseline Patient Characteristics

	Responders	Nonresponders	*P* Values
Patient, n (%)	7 (100)	6 (100)	NS
Age	70±7	69±11	NS
Men, n (%)	4 (57)	6 (100)	NS
NYHA class (II/III/IV)	0/5/2	1/5/0	NS
Minnesota heart failure score	50±32	42±23	NS
LVEF, %	22±6	29±5	NS
LVEDV, mL	199±57	188±32	NS
LVESV, mL	157±50	130±24	NS
Ischemics/nonischemics, n (%)	1 (14)/6 (86)	4 (67)/3 (33)	NS
Sinus rhythm/atrial fibrillation n (%)	4 (57)/3 (43)	3 (50)/3 (50)	NS
QRS duration preimplant, ms	150±28	166±28	NS
QRS duration during CRT, ms	134±19	161±16	NS
QRS morphology (LBBB/RBBB/ nonspecific IVCD), n	5/0/2	6/0/0	NS
Bi-V pacing, %	97±4	97±3	NS
Bisoprolol* n (%)	6 (85)	6 (100)	NS
Amiodarone* n (%)	1 (14)	1 (17)	NS
ACEi/ARB n (%)	7 (100)	6 (100)	NS
Statins n (%)	3 (43)	4 (67)	NS

ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CRT, cardiac resynchronization therapy; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; IVCD, intraventricular conduction delay; LBBB, left bundle-branch block; LV, left ventricular; NS, not significant; NYHA, New York Heart Association; and RBBB, right bundle-branch block.

*During the follow-up, 3 of the 6 patients in the responder group had increased Bisoprolol dosages. None of the patients in the nonresponder group had changed Bisoprolol dosages. The only patient who was on amiodarone in the responder group continued its usage during the follow-up, whereas the only patient who was on amiodarone in the nonresponder group discontinued its usage 2 mo after CRT. These changes in medication could not have accounted for the divergent changes in the activation recovery intervals observed in our study.

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 Unify 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 electrogram (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.[20] 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.[21] 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.[15–19] An example showing the measurement and the stability of recordings is illustrated in Figure 1.

Responders to CRT were defined as those demonstrating a ≥15% 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 χ^2 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. There

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 from 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 LVARI at 6 weeks and 6 months compared with 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.

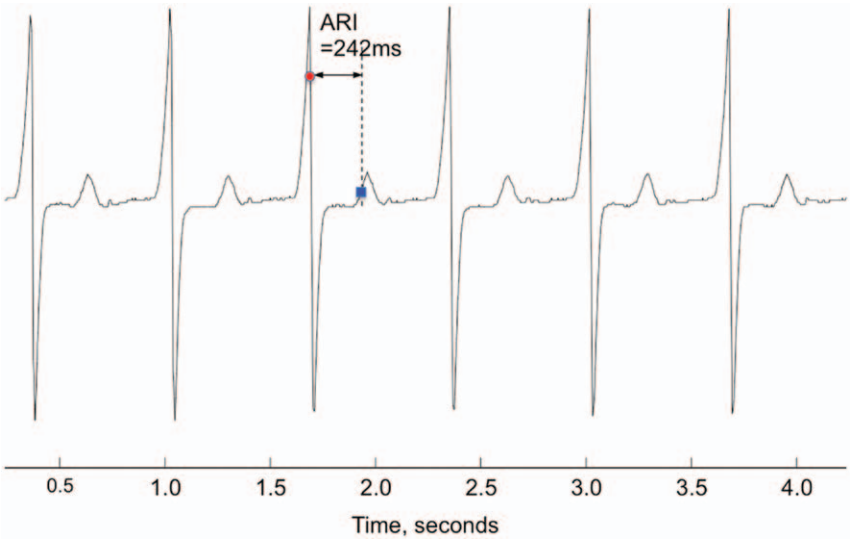

Figure 1. An example of left ventricular unipolar electrogram raw data recording demonstrating activation recovery interval (ARI).

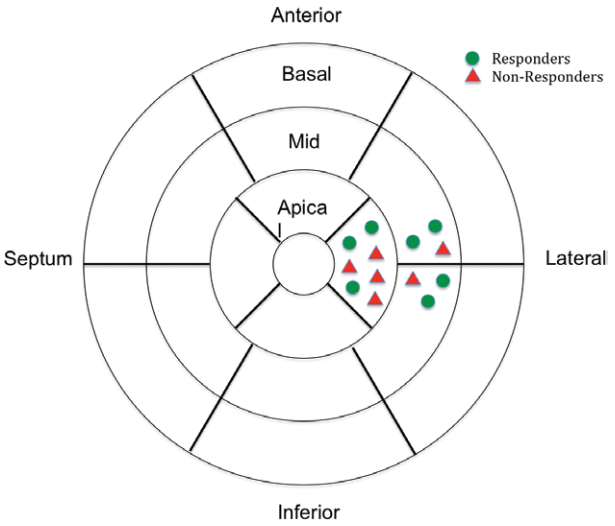

Figure 2. Positions of the left ventricular lead tip where unipolar electrograms are made, according to American Heart Association 17-segment heart model.

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.[10] 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[22] 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, Braunschweig et al[23] 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[24] 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.[25]

Table 2. Patient Clinical and Echocardiographic Indices at 6 Months

	Responders	Nonresponders	*P* Values
Patient, n	7	6	
NYHA class	1.8±0.6	2.6±0.5	<0.01
Minnesota heart failure score	31±23	31±23	NS
LVEF, %	39±7	31±4.5	0.04
LVEDV, mL	157±45	192±29	NS
LVESV, mL	98±37	134±27	NS
Δ LVEDV, %	−20±12	−3±5	<0.01
Δ LVESV, %	−36±15	−3±5	<0.01

Δ denotes % change compared with baseline echocardiographic parameters. EDV indicates end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; LV, left ventricular; NS, not significant; and NYHA, New York Heart Association.

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 Ca^{2+} currents and calcium cycling.[1,10,26,27] Studies of animal models of heart failure have demonstrated that considerable heterogeneity exists in these changes.[28]

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.[29,30] 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,[31] 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.[10,11] These observations suggest that the myocardium can respond to changes in stretch by altering its electric properties through a process of mechano-electric feedback.[10,11,32–34] 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[11] have suggested that this trigger may be mediated through intermediates, including stretch-activated nonselective ion channels,[35,36] cytoskeletal proteins,[37] and stretch-activated signal transduction pathways.[38]

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.[10] 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.[10]

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

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

LV ARI	ms	Responders		Nonresponders	
Day 0	Mean	259±53		253±25	
	Median	238; IQR, 213 to 303		262; IQR, 224 to 270	
Week 6	Mean	255±50	−4±18*	†265±25	13±12*
	Median	252; IQR, 224 to 287	0; IQR, −20 to −11*	†278; IQR, 234 to 284	12; IQR, 7 to 21*
Month 6	Mean	†246±47	−13±12‡	†272±22	19±16‡
	Median	†235; IQR, 215 to 287	−16; IQR, −19 to −2‡	†277; IQR, 258 to 284	17; IQR, 8 to 35‡

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.

caused by altered activation sequence are a component of myocardial memory.[11] 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 LVARI. 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.

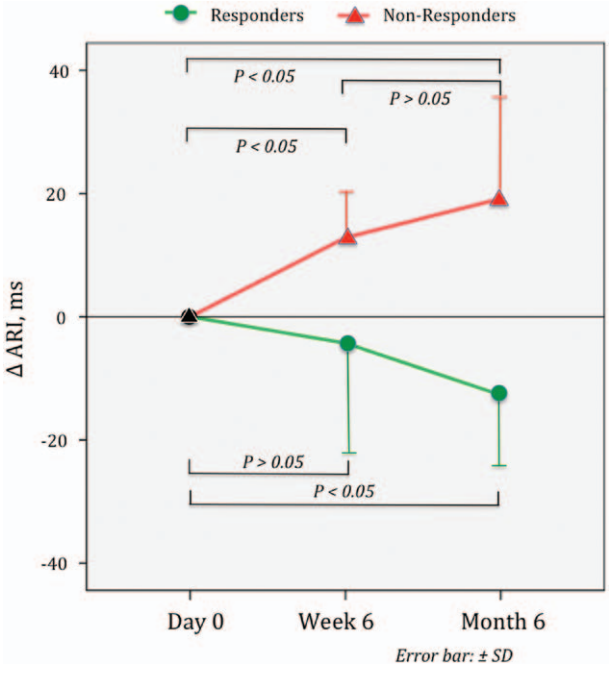

Figure 3. Changes in regional left ventricular activation recovery intervals, Δ activation recovery intervals (ARIs), during right ventricular pacing at day 0, 6 weeks, and 6 months postcardiac resynchronization therapies.

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.[12,13,39–41] 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.[12,13] 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.[11,42] 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.[43]

Reversal of APD lengthening by CRT has been shown experimentally to reduce dispersion and hence be potentially arrhythmia protective.[10] Interpreting our results in this context must remain speculative, as we have no evidence that APD at

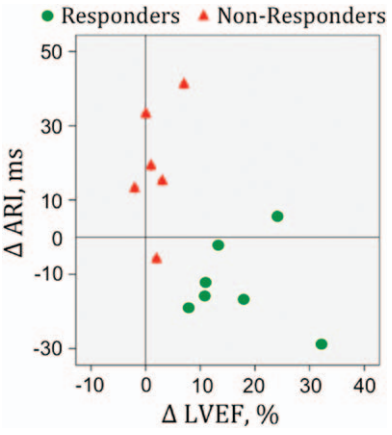

Figure 4. Scatter plots of changes in left ventricular (LV) activation recovery interval (ARI) with changes in LV ejection fraction, from day 0 to 6 months after cardiac resynchronization therapy.

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 arrhythmia 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.

Acknowledgment

We thank Ruben Coronel for helpful discussion on methodology.

Sources of Funding

Z. Chen is supported by a British Heart Foundation Fellowship Grant.

Disclosures

None.

References

1. Aiba T, Tomaselli GF. Electrical remodeling in the failing heart. *Curr Opin Cardiol*. 2010;25:29–36.
2. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NA III, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W; MADIT-CRT Trial Investigators. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med*. 2009;361:1329–1338.
3. Linde C, Abraham WT, Gold MR, St John Sutton M, Ghio S, Daubert C; REVERSE (REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction) Study Group. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. *J Am Coll Cardiol*. 2008;52:1834–1843.
4. Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, Hohnloser SH, Nichol G, Birnie DH, Sapp JL, Yee R, Healey JS, Rouleau JL; Resynchronization-Defibrillation for Ambulatory Heart Failure Trial Investigators. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med*. 2010;363:2385–2395.
5. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L; Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med*. 2005;352:1539–1549.
6. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM; Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med*. 2004;350:2140–2150.
7. Markowitz SM, Lewen JM, Wiggenhorn CJ, Abraham WT, Stein KM, Iwai S, Lerman BB. Relationship of reverse anatomical remodeling and ventricular arrhythmias after cardiac resynchronization. *J Cardiovasc Electrophysiol*. 2009;20:293–298.
8. Rickard J, Popovic Z, Verhaert D, Sraow D, Baranowski B, Martin DO, Lindsay BD, Varma N, Tchou P, Grimm RA, Wilkoff BL, Chung MK. The QRS narrowing index predicts reverse left ventricular remodeling following cardiac resynchronization therapy. *Pacing Clin Electrophysiol*. 2011;34:604–611.
9. Rickard J, Jackson G, Spragg DD, Cronin EM, Baranowski B, Tang WH, Wilkoff BL, Varma N. QRS prolongation induced by cardiac resynchronization therapy correlates with deterioration in left ventricular function. *Heart Rhythm*. 2012;9:1674–1678.
10. Aiba T, Hesketh GG, Barth AS, Liu T, Daya S, Chakir K, Dimaano VL, Abraham TP, O'Rourke B, Akar FG, Kass DA, Tomaselli GF. Electrophysiological consequences of dyssynchronous heart failure and its restoration by resynchronization therapy. *Circulation*. 2009;119:1220–1230.
11. Jeyaraj D, Wilson LD, Zhong J, Flask C, Saffitz JE, Deschênes I, Yu X, Rosenbaum DS. Mechanoelectrical feedback as novel mechanism of cardiac electrical remodeling. *Circulation*. 2007;115:3145–3155.
12. Medina-Ravell VA, Lankipalli RS, Yan GX, Antzelevitch C, Medina-Malpica NA, Medina-Malpica OA, Droogan C, Kowey PR. Effect of epicardial or biventricular pacing to prolong QT interval and increase transmural dispersion of repolarization: does resynchronization therapy pose a risk for patients predisposed to long QT or torsade de pointes? *Circulation*. 2003;107:740–746.
13. Fish JM, Di Diego JM, Nesterenko V, Antzelevitch C. Epicardial activation of left ventricular wall prolongs QT interval and transmural dispersion of repolarization: implications for biventricular pacing. *Circulation*. 2004;109:2136–2142.
14. Cutler MJ, Jeyaraj D, Rosenbaum DS. Cardiac electrical remodeling in health and disease. *Trends Pharmacol Sci*. 2011;32:174–180.
15. Wyatt RF, Burgess ML, Evans AK, Lux RL, Abildskov JA, Tsutsu T. Estimation of ventricular transmembrane action potential durations and repolarization times from unipolar electrograms. *Am J Cardiol*. 1981;47:488.
16. Millar CK, Kralios FA, Lux RL. Correlation between refractory periods and activation-recovery intervals from electrograms: effects of rate and adrenergic interventions. *Circulation*. 1985;72:1372–1379.
17. Haws CW, Lux RL. Correlation between *in vivo* transmembrane action potential durations and activation-recovery intervals from electrograms.

Effects of interventions that alter repolarization time. *Circulation*. 1990;81:281–288.
18. Coronel R, de Bakker JM, Wilms-Schopman FJ, Opthof T, Linnenbank AC, Belterman CN, Janse MJ. Monophasic action potentials and activation recovery intervals as measures of ventricular action potential duration: experimental evidence to resolve some controversies. *Heart Rhythm*. 2006;3:1043–1050.
19. Potse M, Vinet A, Opthof T, Coronel R. Validation of a simple model for the morphology of the T wave in unipolar electrograms. *Am J Physiol Heart Circ Physiol*. 2009;297:H792–H801.
20. Ghosh S, Silva JN, Canham RM, Bowman TM, Zhang J, Rhee EK, Woodard PK, Rudy Y. Electrophysiologic substrate and intraventricular left ventricular dyssynchrony in nonischemic heart failure patients undergoing cardiac resynchronization therapy. *Heart Rhythm*. 2011;8:692–699.
21. Western D, Taggart P, Hanson B. Real-time feedback of dynamic cardiac repolarization properties. *Conf Proc IEEE Eng Med Biol Soc*. 2010;2010:114–117.
22. Wecke L, van Deursen CJ, Bergfeldt L, Prinzen FW. Repolarization changes in patients with heart failure receiving cardiac resynchronization therapy-signs of cardiac memory. *J Electrocardiol*. 2011;44:590–598.
23. Braunschweig F, Pfizenmayer H, Rubulis A, Schoels W, Linde C, Bergfeldt L. Transient repolarization instability following the initiation of cardiac resynchronization therapy. *Europace*. 2011;13:1327–1334.
24. Lellouche N, De Diego C, Boyle NG, Wiener I, Akopyan G, Child JS, Shivkumar K. Relationship between mechanical and electrical remodelling in patients with cardiac resynchronization implanted defibrillators. *Europace*. 2011;13:1180–1187.
25. Kuijpers NH, Hermeling E, Bovendeerd PH, Delhaas T, Prinzen FW. Modeling cardiac electromechanics and mechanoelectrical coupling in dyssynchronous and failing hearts: insight from adaptive computer models. *J Cardiovasc Transl Res*. 2012;5:159–169.
26. Nattel S, Maguy A, Le Bouter S, Yeh YH. Arrhythmogenic ion-channel remodeling in the heart: heart failure, myocardial infarction, and atrial fibrillation. *Physiol Rev*. 2007;87:425–456.
27. Plotnikov AN, Yu H, Geller JC, Gainullin RZ, Chandra P, Patberg KW, Friezema S, Danilo P Jr, Cohen IS, Feinmark SJ, Rosen MR. Role of L-type calcium channels in pacing-induced short-term and long-term cardiac memory in canine heart. *Circulation*. 2003;107:2844–2849.
28. Akar FG, Rosenbaum DS. Transmural electrophysiological heterogeneities underlying arrhythmogenesis in heart failure. *Circ Res*. 2003;93:638–645.
29. Helm RH, Leclercq C, Faris OP, Ozturk C, McVeigh E, Lardo AC, Kass DA. Cardiac dyssynchrony analysis using circumferential versus longitudinal strain: implications for assessing cardiac resynchronization. *Circulation*. 2005;111:2760–2767.
30. Prinzen FW, Hunter WC, Wyman BT, McVeigh ER. Mapping of regional myocardial strain and work during ventricular pacing: experimental study using magnetic resonance imaging tagging. *J Am Coll Cardiol*. 1999;33:1735–1742.
31. Yano M, Kohno M, Konishi M, Takahashi T, Seki K, Matsuzaki M. Influence of left ventricular regional nonuniformity on afterload-dependent relaxation in intact dogs. *Am J Physiol*. 1994;267(1 pt 2):H148–H154.
32. Taggart P, Sutton PM. Cardiac mechano-electric feedback in man: clinical relevance. *Prog Biophys Mol Biol*. 1999;71:139–154.
33. Zabel M, Koller BS, Sachs F, Franz MR. Stretch-induced voltage changes in the isolated beating heart: importance of the timing of stretch and implications for stretch-activated ion channels. *Cardiovasc Res*. 1996;32:120–130.
34. Spragg DD, Akar FG, Helm RH, Tunin RS, Tomaselli GF, Kass DA. Abnormal conduction and repolarization in late-activated myocardium of dyssynchronously contracting hearts. *Cardiovasc Res*. 2005;67:77–86.
35. Martinac B. Mechanosensitive ion channels: molecules of mechanotransduction. *J Cell Sci*. 2004;117(pt 12):2449–2460.
36. Trayanova NA, Constantino J, Gurev V. Models of stretch-activated ventricular arrhythmias. *J Electrocardiol*. 2010;43:479–485.
37. Alenghat FJ, Ingber DE. Mechanotransduction: all signals point to cytoskeleton, matrix, and integrins. *Sci STKE*. 2002;2002:pe6.
38. Sadoshima J, Izumo S. The cellular and molecular response of cardiac myocytes to mechanical stress. *Annu Rev Physiol*. 1997;59:551–571.
39. Thijssen J, Borleffs CJ, Delgado V, van Rees JB, Mooyaart EA, van Bommel RJ, van Erven L, Boersma E, Bax JJ, Schalij MJ. Implantable cardioverter-defibrillator patients who are upgraded and respond to cardiac resynchronization therapy have less ventricular arrhythmias compared with nonresponders. *J Am Coll Cardiol*. 2011;58:2282–2289.
40. Kurita T, Noda T, Aiba T, Nakajima I, Shimizu W, Motoki K, Yasuoka R, Miyazaki S, Kamakura S. Cardiac resynchronization therapy to prevent life-threatening arrhythmias in patients with congestive heart failure. *J Electrocardiol*. 2011;44:736–741.
41. Timóteo AT, Oliveira MM, Silva MN, Toste A, Ramos R, Feliciano J, Cunha PS, Soares R, Santos S, Ferreira RC. [Incidence of ventricular arrhythmias in patients with severe left ventricular systolic dysfunction: is there a benefit after cardiac resynchronization therapy?]. *Rev Port Cardiol*. 2011;30:823–828.
42. Tsvetkova AS, Kibler NA, Nuzhny VP, Shmakov DN, Azarov JE. Acute effects of pacing site on repolarization and haemodynamics of the canine ventricles. *Europace*. 2011;13:889–896.
43. Suzuki A, Shiga T, Nakai K, Futagawa K, Matsuyama Y, Shoda M, Kasanuki H, Hagiwara N. Interlead difference between T-peak to T-end intervals in resynchronization patients with an implantable cardioverter-defibrillator. *J Electrocardiol*. 2010;43:706–712.
44. Hsu JC, Solomon SD, Bourgoun M, McNitt S, Goldenberg I, Klein H, Moss AJ, Foster E; MADIT-CRT Executive Committee. Predictors of super-response to cardiac resynchronization therapy and associated improvement in clinical outcome: the MADIT-CRT (multicenter automatic defibrillator implantation trial with cardiac resynchronization therapy) study. *J Am Coll Cardiol*. 2012;59:2366–2373.
45. Delgado V, Ypenburg C, van Bommel RJ, Tops LF, Mollema SA, Marsan NA, Bleeker GB, Schalij MJ, Bax JJ. Assessment of left ventricular dyssynchrony by speckle tracking strain imaging comparison between longitudinal, circumferential, and radial strain in cardiac resynchronization therapy. *J Am Coll Cardiol*. 2008;51:1944–1952.
46. Knebel F, Schattke S, Bondke H, Walde T, Eddicks S, Reibis R, Baumann G, Borges AC. Evaluation of longitudinal and radial two-dimensional strain imaging versus Doppler tissue echocardiography in predicting long-term response to cardiac resynchronization therapy. *J Am Soc Echocardiogr*. 2007;20:335–341.

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 dyssynchronous 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 dyssynchrony. 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.

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

Zhong Chen, Ben Hanson, Manav Sohal, Eva Sammut, Nick Child, Anoop Shetty, Ryan Boucher, Julian Bostock, Jaswinder Gill, Gerald Carr-White, C. Aldo Rinaldi and Peter Taggart

Circ Arrhythm Electrophysiol. 2013;6:265-271; originally published online March 9, 2013;
doi: 10.1161/CIRCEP.112.000148
Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-3149. Online ISSN: 1941-3084