Correlation of Electrical and Mechanical Reverse Remodeling after Cardiac Resynchronization Therapy

Swapna Kamireddy, M.D., Sunil Kumar Agarwal, M.D., Evan Adelstein, M.D., Sandeep Jain, M.D., and Samir Saba, M.D.

From the Cardiac Electrophysiology Section of the University of Pittsburgh Medical Center, Pittsburgh, PA

Background: Cardiac resynchronization therapy (CRT) improves clinical outcome in many patients with refractory heart failure (HF). This study examined whether CRT is associated with reverse electrical remodeling by surface electrocardiogram (ECG).

Methods: Consecutive CRT recipients at the University of Pittsburgh Medical Center with >90 days of follow-up were included in this analysis. ECG data were abstracted from medical records. Subjects with a relative increase of $\geq 15\%$ in left ventricular ejection fraction (LVEF) after CRT were considered responders.

Results: A total of 113 patients (age 69 ± 11 years, men 70%, white 92%) were followed for a mean duration of 407 ± 290 (92–1439) days. Overall, LVEF increased after CRT ($29 \pm 13\%$ vs $24 \pm 9\%$; $P < 0.01$) and 50% of patients were responders. The mean native QRS interval among responders was higher than in nonresponders (163 ± 32 ms vs 148 ± 29 ms; $P < 0.01$). More than 3 months after CRT, there was no change in the paced QRS duration compared to baseline. Paced QRS duration, however, decreased among responders and increased among nonresponders and was significantly different by response status ($P < 0.001$). There was a significant correlation between increase in LVEF and decrease in paced QRS width in the overall population ($r = -0.3$; $P < 0.01$).

Conclusions: Among responders to CRT, the paced QRS width decreases significantly, whereas it increases among nonresponders. Given the paced nature of the QRS, the improved conduction probably reflects enhanced cell-to-cell coupling after CRT as opposed to improved conduction within the His-Purkinje system. These findings have significant implications as to the mechanisms of benefit from CRT.

Ann Noninvasive Electrocardiol 2009;14(2):153–157

cardiac resynchronization therapy; electrical remodeling; QRS duration; mechanical remodeling; heart failure

Cardiac resynchronization therapy (CRT) has become an integral component of heart failure (HF) management in patients with marked left ventricular dysfunction, intraventricular conduction delay, and severe HF symptoms. HF patients who qualify for this therapy may extract benefit from CRT in the form of improved exercise tolerance, maximal oxygen consumption, quality of life, and echocardiographic measures of reverse mechanical remodeling.^{1,2} They may also enjoy a decreased risk of hospitalization for HF and lower total mortality rates.^{3,4}

A small majority of CRT recipients enjoy improved echocardiographic parameters during follow-up, in the form of increased left ventricular ejection fraction (LVEF), and decreased measures of left ventricular end-systolic and end-diastolic dimensions.⁵ Whether this evidence of reverse mechanical remodeling is accompanied by evidence of electrical remodeling has been suggested by few small and contradictory studies^{6,7} but has not yet been established. Furthermore, if in fact reverse electrical remodeling does occur, it remains uncertain whether it is a direct consequence of

Conflict of interest: none.

Sources of funding: none.

Address for correspondence: Samir Saba, M.D., Director, Cardiac Electrophysiology, University of Pittsburgh, 200 Lothrop Street, PUH B535, Pittsburgh, PA 15213. Fax: 412-647-7979; E-mail: sabas@upmc.edu

©2009, Copyright the Authors
Journal compilation ©2009, Wiley Periodicals, Inc.

the improved mechanics of the ventricles as opposed to being an independent phenomenon. Also, if such reverse electrical remodeling does in fact occur, it remains unclear whether it pertains to the specialized cells of conduction in the His-Purkinjee system or cellular coupling within the ventricular parenchyma.

In this study, we investigated the presence of any evidence for reverse electrical remodeling in the hearts of CRT recipients and examined the correlation of any such electrical remodeling with the echocardiographic response in these patients.

METHODS

Study Population

Consecutive patients implanted with CRT devices at the University of Pittsburgh Medical Center between 2002 and 2006 were included. Patients were excluded if they did not have baseline and follow-up electrocardiographic (ECG) and echocardiographic data. Surface ECGs with native rhythm were obtained prior to CRT implantation in all patients. Paced ECGs were obtained the day after the procedure and in follow-up, more than 3 months after the CRT device implantation. Those with more than 90 days of follow-up paced ECG and echocardiography data were included in this study. Echocardiographic data were obtained before and more than 3 months after the CRT device implantation. The study was approved by the Institutional Review Board of the University of Pittsburgh.

CRT Device Implantation

All device implants were performed at the University of Pittsburgh Medical Center by staff electrophysiologists. Right atrial, right ventricular, and coronary sinus leads were placed transvenously under fluoroscopic guidance. Lateral and posterolateral coronary venous branches were preferentially targeted for left ventricular lead position, with alternative locations accepted in the event of high pacing thresholds, diaphragmatic stimulation, or a lack of suitable venous branches.

Echocardiography

Echocardiography was performed as clinically indicated⁸ with standard parasternal, apical, and subcostal transthoracic views. Studies were read by a core group of university cardiologists. Measurements of left atrial dimension were made in the parasternal long-axis view at end-diastole. Left ventricular end-diastolic diameter was measured just prior to mitral valve closure in the parasternal long-axis view, and left ventricular end-systolic diameter was measured just prior to mitral valve opening. LVEF was visually obtained. Mitral regurgitant severity was graded primarily with color Doppler mapping. Subjects with a relative increase of 15% or more in LVEF after CRT were considered responders.

surements of left atrial dimension were made in the parasternal long-axis view at end-diastole. Left ventricular end-diastolic diameter was measured just prior to mitral valve closure in the parasternal long-axis view, and left ventricular end-systolic diameter was measured just prior to mitral valve opening. LVEF was visually obtained. Mitral regurgitant severity was graded primarily with color Doppler mapping. Subjects with a relative increase of 15% or more in LVEF after CRT were considered responders.

ECG Recording

A 12-lead ECG was recorded on all patients the day after CRT device implantation and then in follow-up. All ECGs were recorded using the GE Marquette Mac 5000 machine (General Electric, Chicago, IL, USA). The QRS width was determined from the computer reading (GE Mac 5000) and was verified manually using calipers at a paper speed of 25 mm/s. The median time between the baseline ECG recording, the day after CRT implantation, and the follow-up ECG was 418 days (92–1439 days). All patients were followed in the device clinic at our institution. Patients with lead dislodgement or noncapture were excluded from this analysis.

Statistical Methods

Means and percentages were used to describe continuous and categorical variables, respectively. Paired *t*-tests were done to compare if there was a difference in the means or differences in the mean of differences of a variable between baseline and follow-up. Pearson correlation coefficients were calculated to find the relationship between electrical and mechanical remodeling. *P* values < 0.05 were considered statistically significant. The SAS software (version 9.1.3, Cary, NC, USA), and STATA/IC version 10 (StataCorp LP, College Station, TX, USA) were used for all statistical analyses.

RESULTS

The baseline characteristics of the 113 patients included in the study are shown in Table 1. The demographics of the enrolled patients are consistent with CRT recipient in published multicenter biventricular pacing trials. Most patients were Caucasian men, with ischemic cardiomyopathy with severe

Table 1. Baseline Characteristics of Study Population by Response Status

Baseline	Total (n = 113)	Responders (n = 57)	Nonresponders (n = 56)	P value
Age (years)	69.3 ± 11.3	69.3 ± 12.3	69.3 ± 10.4	NS
Race (white)	92%	93%	92%	NS
Gender (female)	30%	25%	35%	NS
ICM	73%	70%	75%	NS
LVEF (%)	24.0 ± 9.1	21.8 ± 7.2	26.1 ± 10.4	0.01
LVESD (cm)	5.16 ± 1.22	5.04 ± 1.22	5.28 ± 1.22	NS
LVEDD (cm)	6.12 ± 1.08	5.98 ± 1.03	6.25 ± 1.11	NS
HR (b/min)	82.4 ± 46.5	84.7 ± 51.4	80.2 ± 41.4	NS
PR (ms)	195.4 ± 43.3	191.3 ± 46.8	199.31 ± 40.19	NS
QRS (ms)	155.3 ± 31.1	162.54 ± 31.72	148.14 ± 29.06	0.01
QRS axis (°)	-12.6 ± 60.6	-9.8 ± 61.5	-15.2 ± 60.1	NS
QT (ms)	435.7 ± 56.2	441.4 ± 57.5	430.1 ± 54.8	NS
QTc (ms)	479.6 ± 60.0	473.9 ± 45.3	485.4 ± 71.9	NS

HR = heart rate; ICM = ischemic cardiomyopathy; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter.

heart failure symptoms despite optimal medical therapy. The mean follow-up duration for this cohort was 407 ± 290 days (range = 92–1439 days). About 75% of patients were on β -adrenergic-blocking agents and 65% were on angiotensin-converting enzyme inhibitors or angiotensin receptor inhibitors. There were no differences in the use of these medications between the two study groups (Table 1). Amiodarone was used in only 11 out of 113 patients (10%) equally, with no difference between the study groups.

According to the definition of response to CRT (more than 15% relative increase in LVEF), 50% of patients were considered responders. Compared to nonresponders, responders tended to have a lower baseline LVEF ($21.8 \pm 7.2\%$ vs $26.1 \pm 10.4\%$; $P = 0.01$) and a wider baseline native QRS complex (163 ± 32 ms vs 148 ± 29 ms; $P = 0.01$) (Fig. 1). All other baseline clinical, ECG, and echocardiographic parameters were similar.

Overall, LVEF increased after CRT in the overall cohort ($29 \pm 13\%$ vs $24 \pm 9\%$; $P < 0.01$) more than 3 months after CRT, but there was no change in the paced QRS duration compared to baseline (155.3 ± 31.1 ms at baseline vs 155.2 ± 24.7 ms after CRT; $P = \text{NS}$). Paced QRS duration, however, decreased among responders and increased among nonresponders and was significantly different by response status (-11 ± 33 ms for responders vs 11 ± 31 ms for nonresponders; $P < 0.001$) (Table 2 and Fig. 1). There was also a statistically significant negative correlation between LVEF and paced QRS width in the overall population ($r = -0.3$; $P <$

0.01) (Fig. 2). This negative correlation is driven primarily by the responders (Fig. 3).

DISCUSSION

In this study, we demonstrate evidence of reverse electrical remodeling in responders to CRT by echocardiographic criteria. Patients who enjoy more than 15% increase in their LVEF after CRT tend to have narrowing of their paced QRS complex, suggesting that the reverse electrical remodeling is, at least partially localized to the myocardial

Figure 1. Bar graph showing the change in paced QRS duration after CRT by response status of patients. Note the decrease in paced QRS duration in the responders compared to the nonresponders who actually have an increased paced QRS width.

Table 2. Changes from Baseline in Electrocardiographic and Echocardiographic Parameters during Follow-Up by Response Status

Variable	Responders	Nonresponders	P value
LVEF (%)	69.8 ± 54.6	-15.1 ± 18.5	<0.001
LVEDD (cm)	0.25 ± 0.83	-0.030 ± 0.53	0.13
LVESD (cm)	0.35 ± 0.92	0.05 ± 1.0	0.21
Paced QRS duration (ms)	-11 ± 33	11 ± 31	<0.001
Paced QRS axis	-40 ± 142	-22 ± 112	0.42
Paced QTc duration (ms)	13 ± 81	31 ± 52	0.14

LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter.

parenchyma, presumably reflecting improved cell-to-cell conduction versus ion channel remodeling leading to improved conduction properties.

Henrickson et al.⁶ reported on 25 recipients of biventricular pacing devices with results consistent, although not identical to ours. In their small population, they documented a 7% relative narrowing of the native QRS complex after CRT. This order of magnitude is consistent with the decrease in paced QRS width seen in CRT responders in our study. Unlike our study, however, the site of reverse electrical remodeling is not well defined in

Figure 2. Linear regression showing an inverse relationship between the change in paced QRS width and the change in left ventricular ejection fraction after CRT ($r = -0.30$; $P < 0.01$). The linear regression equation is: change in LVEF = $4.7 - 0.11$ change in QRS width. **Figure 3.** Linear regression showing the relationship between the change in paced QRS width and the change in left ventricular ejection fraction after CRT by response status. Note that the responders had a significant decrease in the width of their paced QRS complex with increasing left ventricular ejection fraction ($r = -0.31$; $P = 0.02$), whereas the nonresponders had an increase in their paced QRS duration with increasing left ventricular ejection fraction ($r = 0.20$; $P = 0.13$). The linear regression equations are: change in LVEF = $13.3 - 0.09$ change in QRS width for the responders and change in LVEF = $-5.2 + 0.05$ change in QRS width for the nonresponders.

the study by Henrickson et al., since a narrower native QRS may represent improved conduction either in the His-Purkinjee system or in the ventricular myocardium, or both. According to our data, the site of improved ventricular conduction is clearly localized in the ventricular myocardium and is seen only in the context of reverse mechanical remodeling. Only 15 out of the 25 patients in the study by Henrickson et al. had full echocardiographic data, rendering the linking of electrical reverse remodeling to mechanical rejuvenation very difficult.

In a more recent study, Stockburger et al.⁷ investigated the same question of reverse electrical remodeling after CRT. In 21 CRT device recipients, they evaluated the change in native QRS width before and after biventricular pacing. Twenty-one other patients with cardiomyopathy but no CRT indication were used as controls. In both groups, they documented an increase in native QRS width from baseline, over the course of follow-up, although the CRT group had, on average, a significant improvement in mean left ventricular end-diastolic dimensions. The results of this study are in clear contradiction with that of Henrickson et al.⁶ and

ours. This may be due to its small size as well as to the fact that it did not distinguish between CRT responders and nonresponders in analyzing what happens to the native QRS complex in follow-up.

The association of improved ventricular mechanics and improved electrical conduction such as we documented in our current study is not surprising. Mechanical stretch has been shown to affect cell-to-cell coupling through both a direct effect on gap junctions' trafficking, synthesis, and degradation, as well as via changes in the composition of the extracellular matrix that may, in turn, affect electrical coupling in cardiac myocytes.⁹⁻¹¹ Improved cell-to-cell coupling may decrease the risk of lethal arrhythmias¹² in sick hearts. If in fact the mechanism responsible for the narrower paced QRS complex in CRT responders turns out to be secondary to improved cell-to-cell coupling, then this may explain the benefit conferred by CRT from the arrhythmic perspective, as suggested by some randomized controlled multicenter trials of CRT therapy.¹³

Our study has few limitations that deserve mentioning. First, it is a retrospective observational study of all recipients of CRT at our institution who had full electrocardiographic and echocardiographic data. Although many patients were excluded based on deficient medical records, it is unlikely that our reported results would have been different had they been included. Second, echocardiographic interpretation was not strictly quantitative, yet all studies were read by a core group of cardiologists at a single institution, minimizing interobserver variability. Furthermore, most community institutions, as well as many academic centers, do not routinely apply quantitative techniques to echocardiographic interpretation because of their cumbersome nature.

In conclusion, we present evidence for reverse electrical remodeling in responders to CRT. The documented improved conduction seems to be localized to the ventricular myocardium rather than the specialized cells of conduction and is likely secondary to the salutary effects of CRT on ventricular mechanics. These findings may have implications

on the arrhythmic risk of CRT responders. Further investigations into the exact cellular mechanisms of reverse electrical remodeling in CRT responders are needed.

REFERENCES

1. Cazeau S, Leclercq C, Lavergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med* 2001;344:873-880.
2. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;346:1845-1853.
3. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;350:2140-2150.
4. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;352:1539-1549.
5. Abraham WT. Cardiac resynchronization therapy. *Prog Cardiovasc Dis* 2006;48:232-238.
6. Henrikson CA, Spragg DD, Cheng A, et al. Evidence for electrical remodeling of the native conduction system with cardiac resynchronization therapy. *Pacing Clin Electrophysiol* 2007;30:591-595.
7. Stockburger M, Nitardy A, Fateh-Moghadam S, et al. Electrical remodeling and cardiac dimensions in patients treated by cardiac resynchronization and heart failure controls. *Pacing Clin Electrophysiol* 2008;31:70-77.
8. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 1989;2:358-367.
9. Saffitz JE, Kleber AG. Effects of mechanical forces and mediators of hypertrophy on remodeling of gap junctions in the heart. *Circ Res* 2004;94:585-591.
10. Wang TL, Tseng YZ, Chang H. Regulation of connexin 43 gene expression by cyclical mechanical stretch in neonatal rat cardiomyocytes. *Biochem Biophys Res Commun* 2000;267:551-557.
11. Kamkin A, Kiseleva I, Lozinsky I, et al. Electrical interaction of mechanosensitive fibroblasts and myocytes in the heart. *Basic Res Cardiol* 2005;100:337-345.
12. Roell W, Lewalter T, Sasse P, et al. Engraftment of connexin 43-expressing cells prevents post-infarct arrhythmia. *Nature* 2007;450:819-824.
13. Lozano I, Bocchiardo M, Achtelek M, et al. Impact of biventricular pacing on mortality in a randomized crossover study of patients with heart failure and ventricular arrhythmias. *Pacing Clin Electrophysiol* 2000;23:1711-1712.