Prediction of Both Electrical and Mechanical Reverse Remodeling on Acute Electrocardiogram Changes After Cardiac Resynchronization Therapy

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Background: The development of both electrical reverse remodeling and mechanical reverse remodeling (ERR+MRR) after cardiac resynchronization therapy (CRT) implantation could reduce the incidence of lethal arrhythmia, hence the prediction of ERR+MRR is clinically important.

Methods and Results: Eighty-three patients (54 male; 67±12 years old) with CRT >6 months were enrolled. ERR was defined as baseline intrinsic QRS duration (iQRSd) shortening ≥10 ms in lead II on ECG after CRT, and MRR as improvement in LVEF ≥25% on echocardiography after CRT. Acute ECG changes were measured by comparing the pre-implant and immediate post-implant ECG. Ventricular arrhythmia episodes, including ventricular tachycardia and ventricular fibrillation, detected by the implanted device were recorded. Patients were classified as ERR only (n=12), MRR only (n=23), ERR+MRR (n=26), or non-responder (ERR− & MRR−, n=22). On multivariate regression analysis, difference between baseline intrinsic QRS and paced QRS duration (ΔQRSd) >35 ms was a significant predictor of ERR+MRR (sensitivity, 68%; specificity, 64%; AUC, 0.7; P=0.003), and paced QTc >443 ms was a negative predictor of ERR+MRR (sensitivity, 78%; specificity, 60%; AUC, 0.7; P=0.002). On Cox proportional hazard modeling, ERR+MRR may reduce risk of ventricular arrhythmia around 70% compared with non-responder (HR, 0.29; 95% CI: 0.13–0.65).

Conclusions: Acute ECG changes after CRT were useful predictors of ERR+MRR. ERR+MRR was also a protective factor for ventricular arrhythmia.

Key Words: Cardiac resynchronization therapy; Electrical reverse remodeling; Mechanical reverse remodeling; Pacing QRS duration; QTc interval

Cardiac resynchronization therapy (CRT) is the standard treatment for heart failure (HF) with baseline QRS morphology matching complete left bundle branch block (CLBBB) with prolonged intrinsic QRS duration (iQRSd).1 Reverse remodeling after CRT might be classified as electrical reverse remodeling (ERR) with shortened iQRSd on electrocardiogram (ECG), or mechanical reverse remodeling (MRR) with improved left ventricular (LV) function. The effects of ERR (manifesting as decrease ≥10–20 ms in iQRSd after CRT) on ventricular arrhythmia are controversial.2 In contrast, MRR is associated with significantly improved clinical outcomes.3 The anti-arrhythmic effect of only MRR (only mechanical reverse remodeling) in patients with moderate-severe HF, however, is still controversial.4 We recently found that both ERR and MRR (ERR+MRR) after CRT had significantly more protective effects on ventricular arrhythmia than MRR only.6 It is therefore clinically important to predict
ERR+MRR after CRT, and hence the aim of this study was to clarify the relationship between acute ECG changes and reverse remodeling after CRT.

**Methods**

**Patients**

Between March 2004 and June 2012, a total of 83 patients (54 male, 29 female; age, 67±12 years; range, 36–89 years) indicated for CRT were included in this study. All the enrolled patients were subsequently followed up at the present clinic for at least 6 months. ECG and echocardiography were performed in all patients before CRT as baseline, and at least 6 months after CRT implantation as follow-up. All-cause mortality and all-cause hospitalization were recorded as clinical events. A total of 71 patients had sinus rhythm and 12 patients had atrial fibrillation on baseline ECG. Indications for device implantation were based on the current guideline: (1) symptomatic HF with New York Heart Association (NYHA) class III–IV, despite optimal medical treatment (angiotensin-converting enzyme inhibitors, β-blockers, spironolactone, and furosemide); (2) sinus rhythm with left bundle branch abnormality configuration, defined as a wide QRS complex (≥120ms) with rS complex (small R wave, deep S wave) or QS morphology (deep Q/S wave with no preceding R wave) at V1–V2 precordial leads on baseline ECG; and (3) LV ejection fraction (LVEF) ≤35%. Exclusion criteria were: (1) scheduled heart transplantation; (2) reversible cardiomyopathy; and (3) significant comorbidity that decreases life expectancy. Indication for cardiac resynchronization therapy defibrillator (CRT-D) was regulated strictly by the Taiwan National Health Insurance (TNHI), and the CRT-D was only permitted to pay in patients with evidence of coexisting ventricular tachycardia/ventricular fibrillation (VT/VF) and HF. Therefore, few patients received CRT-D (n=11), and the others received CRT pacemaker alone (n=72), manufactured by either St. Jude or Medtronic. In addition to standard implantation of the right atrium (RA) and right ventricular (RV) leads, the LV leads were preferably placed in the LV lateral or posterolateral wall.

The study protocol was approved by the hospital ethics committee and written informed consent was obtained from all patients.

**Implantation**

For all patients, devices were implanted in the electrophysiology laboratory under appropriate sedation, anesthetics and antibiotics. CRT was implanted via subclavian venous puncture under fluoroscopy guidance. Implantation was carried out of either cardiac resynchronization therapy pacemaker (CRT-P) or CRT-D connected via separate ports to transvenous leads placed in the RA, RV, and LV in a lateral tributary of the coronary sinus (CS) to stimulate the LV. First, the RV lead was placed at the RV apex or low inter-ventricular septum to avoid complete atrio-ventricular block (AVB) due to right bundle or His bundle trauma while accessing the CS ostium. The RV lead could contour the tricuspid annulus, which provided an anatomic reference to the CS ostium.

During CS angiography, CS guiding catheter was used to cannulate the CS facilitated by inserting steerable electrophysiology (EP) catheter and guided by RV lead. Local CS electrograms were recorded to analyze the characteristics between the RV (only ventricular local potential) and CS (both atrial and ventricular local potentials). The CS occluded balloon catheter was then inserted after withdrawing the EP catheter. Retrograde radiopaque contrast injection was then used after inflation of the balloon catheter to delineate the coronary venous anatomy. CS venography was done in the left anterior oblique (LAO) 20° and caudal 20° views after 10–20mL contrast media.

The LV leads were inserted through the lateral tributary veins of the CS. Devices were placed in a subcutaneous pocket localized in the pectoral region. All pockets were formed prior to lead implantation after appropriate electrosurgery or sutures. Comprehensive device diagnostics were performed in all leads to confirm the appropriate sensing, pacing thresholds, and impedance parameters. After completion of the procedure, quick optimization of the CRT setting for the AV and VV interval was routinely performed.

**ECG Parameters**

The ECG variables were measured on baseline pre-implant ECG and on the immediate post-implant ECG. iQRSd was measured from the beginning to the end of QRS on all leads. After >6 months of CRT, iQRSd was measured during transient turn-off of bi-ventricular pacing (Figure 1B2).

In the present study, baseline QRS morphology consisted only of LBBB, and the widest QRS duration was chosen before CRT (Figure 1A1). Paced QRSd was measured in all leads and the widest paced QRSd was chosen after CRT pacing (Figure 1B1). The difference between the baseline widest and the paced widest QRS duration was defined as ΔQRSd (baseline intrinsic QRSd–paced QRSd). The measurement of QTc interval in atrial fibrillation was obtained from the average of 3 consecutive beats, as in the previous study. All ECG were recorded at 25mm/s with an amplification of 10mm/mV. In the previous study, lateral lead (V6) was selected for analysis of QT interval because...
of the benefit of predicting cardiac arrhythmic death.\textsuperscript{15} QT interval was measured from the beginning of the QRS complex to the end of the T wave. The end of the T wave was defined as the intersection of the tangent to the steepest downslope of the T-wave and the isoelectric line.\textsuperscript{16} QTc was defined as QT interval corrected with the Bazett formula (QT/RR).\textsuperscript{17} All ECG measurements were performed independently by 2 blinded physicians. When measurements were not identical, the mean was calculated. If the value of mean differed by >10 ms, the measurements were adjudicated by another electrophysiologist.

**Transthoracic Echocardiography**

All patients underwent transthoracic echocardiography on average 97 days (median, 42 days) before CRT implantation. This was done on a clinical echocardiography system (Philips iE33 Ultrasound system, USA), using a sector array probe (S5-1, 1–5 mHz) by a single observer. End-diastolic LV internal diameter (LVIDd) and end-systolic LV internal diameter (LVIDs) were measured in the standard parasternal short axis view. LVEF was calculated using the modified Simpson’s rule on apical 2- and 4-chamber views.

**Definition of ERR and MRR**

ERR was defined as iQRS interval shortening ≥10 ms in lead II after CRT implantation compared with baseline iQRSd. Improvement in LVEF ≥25% after CRT implantation was defined as MRR.\textsuperscript{18,20} Although LV dimension and LV volume are good indices for defining MRR, LVEF was used in the present study, for 3 reasons. First, the primary endpoint in the present study was occurrence of ventricular arrhythmia, and poor LVEF is a major risk factor of ventricular arrhythmia.\textsuperscript{21–23} Second, the relative increase of LVEF and reduction of end-systolic LV volume have equal value in predicting response after CRT implantation.\textsuperscript{24} And third, the reproducibility of echocardiography measurement of LV volume may be limited because of inter-observer variability in the degree of LV shortening on apical view.\textsuperscript{25} In our experience and in previous studies, measurement of LVEF was less affected by inter- and intra-observer variability.\textsuperscript{21}

**Definition of Clinical Events**

All-cause hospitalization was defined as the sum of the total number of hospitalizations (including all relevant and non-relevant events) individually during the period of study. Similarly, all-cause mortality was recorded as the number of deaths (including all relevant and non-relevant deaths). All CRT devices permitted full disclosure of arrhythmia, including VT and VF. VT was defined as cardiac tachyarrhythmia ≥3 beats in duration emanating from the ventricles at a rate of ≥100 beats/min. If VT lasted ≥30 s or was terminated by implantable cardioverter defibrillator (ICD) shock or ATP injection before that time, it was...
termed “sustained VT”. If VT lasted <30s and terminated spontaneously, without associated hemodynamically significant symptoms or rate ≥100beats/min, it was termed “non-sustained VT”. Both sustained and non-sustained VT were considered as VT in this study. VF was defined as cardiac arrhythmia arising from the ventricles that

Table 2. Electrical and Echocardiographic Characteristics

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Non-(ERR+MRR)</th>
<th>ERR+MRR (n=26)</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>iQRSd before CRT (ms)</td>
<td>182±39</td>
<td>169±20</td>
<td>173±20</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>25.7±5.3</td>
<td>19.8±5.8</td>
<td>23.8±5.4</td>
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<td>Non-(ERR+MRR) vs. (ERR+MRR)</td>
<td>22.6±5.9</td>
<td>21.5±6.5</td>
<td>0.47</td>
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<tr>
<td>Pre-QTc(V6) (ms)</td>
<td>557±93</td>
<td>508±57</td>
<td>529±57</td>
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</table>

Acute ECG change after CRT

<table>
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<tr>
<th>Parameters</th>
<th>Non-(ERR+MRR)</th>
<th>ERR+MRR (n=26)</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>Paced QRSd (ms)</td>
<td>143±30</td>
<td>149±20</td>
<td>154±20</td>
</tr>
<tr>
<td>ΔQRSd (ms)</td>
<td>38±42</td>
<td>21±29</td>
<td>19±23</td>
</tr>
<tr>
<td>Paced QTc(V6) (ms)</td>
<td>483±51</td>
<td>462±35</td>
<td>479±41</td>
</tr>
<tr>
<td>ΔQTc(V6) (ms)</td>
<td>74±106</td>
<td>46±68</td>
<td>65±82</td>
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</tbody>
</table>

Echocardiography

| ΔLVEF (%) | 5.4±6 | 16±9 | 1.7±5 | 20±9 | <0.01*† |
| ΔLVIDd (mm) | −0.7±6 | 4.4±7 | 3.9±9 | 8.4±10 | 0.03*† |
| ΔLVIDs (mm) | −3.7±23 | 7.5±9 | 9±16 | 16±14 | <0.01*† |

Outcome

| VT/VF episodes (after CRT) | 0.8±0.5 | 0.7±0.5 | 0.9±0.4 | 0.3±0.5 | <0.01*† |
| All-cause hospitalization | 4±4.7 | 2±2.2 | 0.9±1.7 | 0.8±1 | <0.01*† |
| All-cause mortality (n) | 4 | 2 | 2 | 1.17 | 0.17 |

Table 3. Independent Predictors of ERR+MRR

<table>
<thead>
<tr>
<th>Variables</th>
<th>B</th>
<th>SE</th>
<th>Significance</th>
<th>Exp(B)</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>Univariable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Paced QRSd</td>
<td>−0.41</td>
<td>0.014</td>
<td>0.003*</td>
<td>0.959</td>
<td>0.933–0.986</td>
</tr>
<tr>
<td>ΔQRSd</td>
<td>0.027</td>
<td>0.01</td>
<td>0.005*</td>
<td>1.027</td>
<td>1.008–1.046</td>
</tr>
<tr>
<td>Paced QTc</td>
<td>−0.017</td>
<td>0.007</td>
<td>0.01*</td>
<td>0.983</td>
<td>0.97–0.996</td>
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<tr>
<td>ΔLVEF (%)</td>
<td>−0.105</td>
<td>0.028</td>
<td>&lt;0.001*</td>
<td>0.9</td>
<td>0.851–0.951</td>
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<tr>
<td>ΔLVIDd (mm)</td>
<td>0.071</td>
<td>0.03</td>
<td>0.018*</td>
<td>1.074</td>
<td>1.012–1.139</td>
</tr>
<tr>
<td>ΔLVIDs (mm)</td>
<td>0.041</td>
<td>0.017</td>
<td>0.015*</td>
<td>1.042</td>
<td>1.008–1.076</td>
</tr>
<tr>
<td>Multivariable†</td>
<td></td>
<td></td>
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<tr>
<td>ΔQRSd</td>
<td>0.024</td>
<td>0.01</td>
<td>0.02*</td>
<td>1.024</td>
<td>1.004–1.046</td>
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<tr>
<td>Paced QTc</td>
<td>−0.015</td>
<td>0.007</td>
<td>0.035*</td>
<td>0.985</td>
<td>0.972–0.999</td>
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<tr>
<td>ΔLVEF (%)</td>
<td>−0.147</td>
<td>0.044</td>
<td>0.001*</td>
<td>0.863</td>
<td>0.792–0.940</td>
</tr>
<tr>
<td>ΔLVIDd (mm)</td>
<td>0.046</td>
<td>0.018</td>
<td>0.012*</td>
<td>1.047</td>
<td>1.010–1.086</td>
</tr>
</tbody>
</table>

*P<0.05. †Adjusted for age, sex, and type of cardiomyopathy. ‡Late echocardiographic outcome parameters, excluded from the predictive model. QRSd, QRS duration. Other abbreviations as in Tables 1,2.
occurred when the heart’s electrical activity became disordered and rapid. Episodes of VT and/or VF detected by the implanted device were validated by 2 electrophysiologists.

**Statistical Analysis**

All continuous data are presented as mean±SD. Comparison of the parametric data was done using independent Student’s t-test and ANOVA. P<0.05 was considered statistically significant. Categorical data were compared using chi-squared test. Multiple logistic regression analysis of the acute ECG change parameters was performed for independent predictors of ERR+MRR. Receiver operating characteristic (ROC) curve analysis was used to generate optimal cut-offs with the best accuracy. The area under the diagonal line is 0.5 of the total area. The cut-off point for a general optimal test, which is called the optimal diagnostic point, is on the curve that is the closest to the top of the left-hand y-axis. We used Pythagoras’ theorem to determine the minimum distance, which is the cut-off point: \[ \text{distance} = (1-\text{sensitivity})^2 + (1-\text{specificity})^2 \]. The likelihood ratio (LR) was defined as the likelihood of a positive result in people with disease/likelihood of a positive result in people without disease. Pearson’s correlation analysis was used to assess the relationship between 2 variables. Significant collinearity occurred among these parameters if the variable with tolerance <1−R² was not suitable to be included in the model. Kaplan-Meier survival analysis was used to compare times to event between the 4 groups on log-rank test. Multivariable analysis was done using Cox proportional hazard modeling. Statistical analysis was carried out using SPSS (IBM SPSS Statistics for Windows, version 23.0. IBM Corp, Armonk, NY, USA).

**Results**

**Acute ECG Change vs. Level of Reverse Remodeling**

According to the levels of reverse remodeling, the patients were classified as ERR only (n=12), MRR only (n=23), ERR+MRR (n=26) or non-responder (n=22). Table 1 lists the clinical characteristics and Table 2 lists the assessed parameters for the 4 groups of patients. The ERR+MRR group had significantly lower paced QRSd and paced QTc, but notably greater ΔLVEF, ΔLVIDd, ΔLVIDs, and ΔQRSd. Furthermore, a remarkable reduction in the number of VT/VF episodes and all-cause hospitalizations after CRT was noted. There was no significant difference in gender, age, ischemic cardiomyopathy, iQRSd before CRT or all-cause mortality between the 4 groups.

For predicting ERR+MRR using ECG or echocardiographic parameters, ΔQRSd, ΔLVEF, ΔLVIDd and ΔLVIDs were significant independent positive predictors and paced QTc was a negative predictor on univariate regression. On multivariate regression analysis, only ΔQRSd was an independent positive predictor and paced QTc the negative predictor (Table 3). Multi-collinearity was evaluated on multiple linear regression and binary correlation. There was a high correlation (r>0.5, P<0.05) between ΔLVIDd and ΔLVIDs, paced QTc and paced QT, ΔQRSd and paced QRSd. The outcome (e.g., late echocardiographic outcomes) and discrimination criteria (e.g., ΔLVEF) were excluded in the prediction model. On multiple linear regression, we evaluated multi-collinearity according to tolerance <1−R² (1−R²=0.63 in the present case). Therefore if tolerance <0.63 then the factor was not suitable to be included in the model. The tolerance of ΔLVEF, ΔLVIDd, and ΔLVIDs was 0.59, 0.36, and 0.26, respectively. Therefore, these parameters were excluded from statistical analysis.

On ROC curve analysis, the optimal cut-off was >35 ms for ΔQRSd to predict ERR+MRR (sensitivity, 68%; specificity, 64%; area under the curve [AUC], 0.7; P=0.003), and
was >443 ms for pacing QTc as a negative predictor (sensitivity, 78%; specificity, 60%; AUC, 0.7; P=0.002; Figure 2).

The LR of both ERR+MRR and non-ERR+MRR was closely associated with $\Delta$QRSd and paced QTc interval, respectively. This meant that the patients with greater $\Delta$QRSd were more likely to have ERR+MRR. In contrast, those with longer paced QTc interval were less likely to have MRR+ERR (Table 3).

**Level of Reverse Remodeling vs. VT/VF**
The average time of occurrence of VT/VF was 36.5 months, the median time was 21.5 months and the occurrence of VT/VF was noted in 9 of 26 patients with ERR+MRR (34.6%), in 15 of 23 patients with MRR only (65.2%), in 9 of 12 patients (75.2%) with ERR only, and in 19 of 22 non-responders (86.3%) during the follow-up period (Figure 3). On Cox proportional hazard modeling modified by age and sex, the HR for ERR+MRR, MRR only and ERR only for ventricular arrhythmia were 0.29 (95% CI: 0.13–0.65), 0.6 (95% CI: 0.30–1.20) and 0.68 (95% CI: 0.30–1.53), respectively. Furthermore, all-cause hospitalization was significantly lower in the ERR+MRR group than the others. There was no significant difference in all-cause mortality between the 4 groups.

**Discussion**

**Major Findings**

After CRT implantation, the prediction of ERR+MRR is clinically important. In the present study, one of the major findings was that $\Delta$QRSd >35 ms immediately after CRT pacing was a significant predictor of ERR+MRR with a sensitivity of 68%, specificity of 64% and AUC of 0.7 (P=0.003). In addition, paced QTc interval >443 ms was a negative predictor with a sensitivity of 78%, specificity of 60% and AUC of 0.7 (P=0.002).

The other major finding was that ERR+MRR could reduce the occurrence of ventricular arrhythmia. In previous studies, the anti-arrhythmic effects of ERR were controversial.22–28 The present finding is similar to a previous study in which the CRT-induced MRR and ERR group had a lower rate of appropriate ICD therapy following CRT.29

**Shortened Paced QRSd ($\Delta$QRSd) Can Predict ERR+MRR**

Patients with advanced HF developed significant interventricular and intraventricular conduction delays. Prolonged QRS interval is associated with increased long-term mortality in HF patients.30 Absolute paced QRSd and $\Delta$QRSd are the critical ECG parameters associated with supraventricular arrhythmia in CRT.31 Longer paced QRSd after CRT was shown to dramatically increase the risk of sustained ventricular tachyarrhythmia.32 According to Hsing et al, paced QRSd and $\Delta$QRSd predicted favorable outcomes and CRT responses.33 The beneficial effect of QRS narrowing on reduction of functional mitral regurgitation has been established. Shortened paced QRSd and greater $\Delta$QRSd, especially $\Delta$QRSd ≥20 ms, reflect greater functional mitral regurgitation improvement, higher CRT response rate, and lower rates of death and hospitalization.34 In the present study, only QRSd was chosen because it had a close association with paced QRSd (Pearson correlation, r=0.63, P<0.001), and because $\Delta$QRSd had higher accuracy than paced QRSd (76% vs. 73%) on logistic multivariate regression analysis. ERR+MRR improved LV remodeling and led to a more favorable mitral geometry. The present study also confirmed that the greater the shortening of QRS duration after CRT, the better the survival thereafter.

**Negative Prediction of ERR+MRR With Prolonged Paced QTc**

In the Friedman et al study, larger LV diameter was a powerful predictor of ventricular arrhythmia for patients who received CRT with defibrillator.32 QT interval has a significantly positive correlation with LV dimensions as was also noted in the present study. In the present analysis, paced QTc interval had a significant positive correlation with LV size (i.e. LVIDd) after CRT ($r=0.22$, $P<0.05$). This suggests that the longer paced QTc is associated with bigger LV after CRT. In addition, paced QTc was negatively correlated with LVIDd ($r=-0.24$, $P=0.03$) and $\Delta$LVIDd ($r=-0.26$, $P=0.02$). This means that longer paced QTc is indicative of less LV remodeling after CRT.

Pacing-induced increase of QTc is related to sustained ventricular arrhythmia in patients with CRT.32 Also, prolongation of QT interval is a critical risk factor for ventricular arrhythmia and death in patients with diabetes and ischemic heart disease.33 Therefore, prolonged paced QTc interval not only reflects the negative predictive ability of ERR+MRR but is also associated with a high incidence of ventricular arrhythmia.

**Study Limitations**

This study was limited by the small number of subjects, due to the single-center study design. A multicenter study utilizing nationwide registration is therefore needed to confirm the present results.

**Conclusions**

After CRT implantation, acute ECG changes with $\Delta$QRSd >35 ms can predict ERR+MRR, and pace QTc interval is a negative predictor. Appropriate prediction of ERR+MRR could contribute to reduce the occurrence of lethal ventricular arrhythmia.

**Disclosures**

The authors declare no conflict of interest.

**Acknowledgments**

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Prediction of ERR and MRR by ECG After CRT


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