Limitations and Problems of Assessment of Mechanical Dyssynchrony in Determining Cardiac Resynchronization Therapy Indication

– Is Assessment of Mechanical Dyssynchrony Necessary in Determining CRT Indication? (Con) –

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Contraction delay of the lateral left ventricular free wall can be improved by biventricular pacing. Cardiac resynchronization therapy (CRT) is based on the principle of resynchronizing un-uniformed contraction of the ventricle. Prolongation of the QRS duration on an electrocardiogram served as an indirect marker to identify mechanical dyssynchrony. One of the greatest problems is approximately 30% of the patients who met the criteria do not respond for CRT. One possible explanation for the lack of response for CRT could be the absence of sufficient dyssynchrony to allow the therapy to have any impact. Direct assessments of mechanical dyssynchrony might better select responder patients for CRT. However, RethinQ study demonstrated that patients with heart failure and narrow QRS intervals might not benefit from CRT, even with dyssynchrony. Moreover, the results of the PROSPECT study suggest given the modest sensitivity and specificity in the multicenter setting, despite training and central analysis, no single echocardiographic measurement of dyssynchrony could be recommended to improve patient selection for CRT beyond current guidelines. At present, assessment of mechanical dyssynchrony is not necessary in determining CRT indication. Current indication including QRS width is recommended as selection criteria to identify patients suitable for CRT. (Circ J 2011; 75: 465–471)

Key Words: Cardiac resynchronization therapy; Echocardiography; Heart failure; Pacemakers

Cardiac Resynchronization Therapy (CRT)

Patients with left ventricular (LV) systolic dysfunction and dilation frequently have ventricular contraction delay. Prolonged QRS duration is associated with abnormal activation. The conduction abnormality is associated with delayed depolarization and contraction of the lateral LV free wall. Sometimes a left bundle branch block has been developed in patients with severe heart failure. Contraction delay of the lateral LV free wall is increased by a left bundle branch block. Contraction delay of the lateral LV free wall can be improved by biventricular pacing. CRT is based on the principle of resynchronizing un-uniformed contraction of the ventricle. CRT improves the cardiac function, heart failure hospitalization, quality of life, exercise capacity and overall prognosis of patients suffering from heart failure. In addition, CRT reverses LV remodeling. The implantation of a CRT system is recommended for heart failure patients who remain in symptomatic New York Heart Association (NYHA) functional class III or IV despite optimal medical treatment with low LV ejection fraction ≤35% and a QRS duration ≥120 ms (130 ms in Japan). Prolongation of the QRS duration on an electrocardiogram (ECG) served as an indirect marker to identify mechanical dyssynchrony. However, approximately 30% of the patients who met the criteria do not respond to CRT. The multicenter InSync randomized clinical evaluation (MIRACLE) trial demonstrated that 35% of patients receiving CRT experienced no improvement in the heart failure clinical composite score. No reverse remodeling is observed up to 40% in recent studies based on echocardiographic observation. As ventricular pacing, even biventricular pacing, reduces contractility, existence of dyssynchrony is essential for CRT. One possible explanation for the lack of response for CRT could be the absence of sufficient dyssynchrony to allow the therapy to have any impact. Direct assessments of mechanical dyssynchrony might better select responder patients for CRT. Presence of scar tissue have also great impacts on the effect of CRT. For these purposes,
Prevalence of Dyssynchrony and Efficacy of CRT in Patients With Heart Failure and With Narrow QRS

Dyssynchrony is found not only in patients with heart failure and with wide QRS but also in patients with heart failure and with normal QRS duration.12,33

Yu and colleges reported that a high incidence of mechanical dyssynchrony was found in patients with heart failure and narrow QRS (<120 ms) and 45 patients had heart failure and wide QRS (≥120 ms) and 88 served as normal controls. Echocardiography with tissue Doppler imaging was performed using a 6 basal and 6 mid-segment model. When a maximal difference of Ts of >100 ms was used to define significant systolic asynchrony, it was not found in the control group but was present in 34 (51%) patients in narrow QRS group and 33 (73%) in wide QRS group (χ²=83.2, P<0.001). When a Ts-SD of >32.6 ms was used to define significant systolic asynchrony, it was present in only 3 (3%) control subjects but in 29 (43%) patients in the narrow QRS group and 29 (64%) in the wide QRS group (χ²=58.3, P<0.001). Systolic asynchrony was more prevalent in patients with wide QRS than in those with narrow QRS complexes by both maximal difference in Ts (χ²=5.7, P<0.02) and Ts-SD (χ²=4.8, P<0.03). They concluded that QRS complexes duration is not a determinant of systolic asynchrony and assessment of intraventricular asynchrony is probably more important than QRS duration in considering CRT.

To evaluate the role of CRT in patients with heart failure and with narrow QRS complexes and echocardiographic evidence of mechanical asynchrony, a total of 102 heart failure patients with NYHA functional class III or IV were enrolled. Among them 51 patients had narrow QRS (<120 ms). Tissue Doppler imaging was used to select patients with systolic asynchrony in the narrow QRS group. Clinical and echocardiographic assessments were performed at baseline and 3 months after CRT. There was a significant reduction of LV end-systolic volume in both narrow (122±42 vs. 103±47 ml, P<0.001) and wide QRS narrow (146±74 vs. 112±64 ml, P<0.001) QRS groups. CRT for heart failure patients with narrow QRS complexes and coexisting mechanical asynchrony by tissue Doppler imaging results in LV reverse remodeling.33

RethinQ Study

Although the indications for CRT include a prolonged QRS duration ≥120 or 130 ms in addition of other functional criterias, some patients with narrow QRS complexes have echocardiographic evidence of LV mechanical dyssynchrony and might also benefit from CRT. Only small, single-center studies have suggested that patients with mechanical dyssynchrony and narrow QRS interval might also benefit from CRT. RethinQ (the cardiac resynchronization therapy in patients with heart failure and narrow QRS) study36 was double-blinded clinical trial evaluating the efficacy of CRT in patients with a standard indication for an implantable cardioverter-defibrillator. Subjects were 172 patients who had standard indication for an implantable cardioverter-defibrillator, ie, ischemic or non-ischemic cardiomyopathy and an ejection fraction ≤35%, NYHA class III heart failure, QRS interval ≤130 ms and evidence of mechanical dyssynchrony as measured by echocardiography. Patients received the CRT device and were randomly assigned to the CRT group or to a control group (no CRT) for 6 months. The primary endpoint was the proportion of patients with an increase in peak oxygen consumption of at least 10 ml per kilogram of body weight per minute during cardiopulmonary exercise testing at 6 months. The CRT group and the control group did not differ significantly in the proportion of patients with the primary endpoint (46% and 41%, respectively) at 6 months. In a prespecified subgroup with a QRS interval ≥120 ms, the peak oxygen consumption increased in the CRT group (P=0.02), but it was unchanged in a subgroup with a QRS interval <120 ms (P=0.45). There were 24 heart failure events requiring intravenous therapy in 14 patients in the CRT group (16.1%) and 41 events in 19 patients in the control group (21%), but the difference was no significant. CRT did not improve peak oxygen consumption in patients with moderate-to-severe heart failure, providing evidence that patients with heart failure and narrow QRS intervals might not benefit from CRT. However, a subgroup of patients with a QRS interval of 120 ms to 130 ms did benefit from CRT.

PROSPECT Study

Predictors of response to cardiac resynchronization therapy (PROSPECT) study36,37 is a prospective, multicenter, non-randomized study to evaluate whether specific echocardiographic measurement of dyssynchrony could be used to help predict CRT response. A total of 498 patients with standard CRT indications (NYHA class III or IV heart failure despite the optimal medical therapy, LV ejection fraction ≤35%, QRS ≥130 ms) were enrolled in 53 centers in Europe, Hong Kong and the USA. Twelve echocardiographic parameters of dyssynchrony, based on both conventional and Doppler based methods, were evaluated after site training in acquisition methods and blinded core laboratory analysis. Definitions of positive CRT response were improved clinical composite score and ≥15% reduction in LV end-systolic volume as the parameter of reverse remodeling at 6 months. Clinical composite score was improved in 69% of 426 patients, whereas LV end-systolic volume decreased ≥15% in 56% of 286 patients with paired data. The ability of the 12 echocardiographic parameters to predict clinical composite score response varied widely, with sensitivity ranging from 6% to 74% and specificity ranging from 35% to 91%; for predicting LV end-systolic volume response, sensitivity ranged from 9% to 77% and specificity from 31% to 93%. Three of the echo parameters (IVMD, LVFT/RR and LPEI) were predictors of a small but significant improvement in the clinical composite score and 5 echo measures (SPWMD, IVMD, LVFT/RR, LPEI and Ts-lat-sep) were predictors of reverse remodeling. However, all had low sensitivity and specificity. For all the parameters, the area under the receiver-operating characteristics curve for positive clinical or volume response to CRT was ≤0.62. There was large variability in the analysis of dyssynchrony parameters. Their inter-core laboratories variability was relatively high at 6.5–72%, indicating a need for refinement of the methodology. Results of the PROSPECT study suggest given the modest sensitivity and specificity in the multicenter setting despite training and central analysis, no single echocardiographic measurement of dyssynchrony could be recommended.
to improve patient selection for CRT beyond current guidelines. Efforts aimed at reducing variability arising from technical and interpretative factors might improve the predictive power of these echocardiographic parameters in a broad clinical setting.

**DESIRE Study**

Although QRS duration in inclusion criteria of the most recent studies is 120 ms, mean duration of QRS of patients actually enrolled in these studies was approximately 160 ms. The aim of the DESIRE study was to identify potential long-term responders to CRT on the basis of simple echocardiographic studies of dyssynchrony in patients with QRS duration <150 ms. The study enrolled 64 patients (64.2 ± 12.5 years old). Mean LV ejection fraction was 27 ± 8% and mean LV end-diastolic diameter was 69 ± 9 mm. A total of 56 patients were in NYHA functional class III and 8 in class IV. An ischemic cardiomyopathy was diagnosed in 27 patients and a dilated cardiomyopathy was diagnosed in 37 patients. All patients were implanted with a CRT system and followed for 1 year. Implantation was preceded and followed by clinical, functional and Doppler echocardiographic evaluation. Four patients were excluded from the study due to unsuccessful LV lead implantation (n=1) and unsatisfactory base line echocardiographic images (n=3). Therefore, 60 patients underwent complete follow-up. The primary combined endpoint included (1) death from any cause, (2) heart failure related hospitalization, and (3) NYHA class at 6 months. Before implantation, 27 patients had ≥1 echocardiographic criterion of mechanical dyssynchrony (DES+ group) and 33 had no evidence of dyssynchrony (DES− group). As regards to the primary end-point at 6 months, 33 patients (55%) had improved, 10 (16%) were unchanged and 17 (29%) had deteriorated. Clinical improvement was observed in 19 of 27 DES+ (70%), versus 14 of 33 DES− (42%) patients (P<0.04). Baseline QRS duration did not predict a response to CRT. They concluded that the presence of mechanical dyssynchrony at baseline Doppler echocardiographic examinations predicted 6-months clinical response to CRT in heart failure patients with QRS duration <150 ms.

**Statement From the American Society of Echocardiography and the Heart Rhythm Society**

After the results of several studies including PROSPECT, expert consensus statement from the American Society of Echocardiography endorsed by the Heart Rhythm Society has been published. The writing group does not recommend that patients who meet accepted criteria for CRT should have therapy withheld because of the results of an echocardiographic Doppler dyssynchrony study. They advise that the dyssynchrony reporting should not include a recommendation whether a patient should undergo CRT, as this should be a
clinical decision on a case-by-case basis for these borderline or challenging cases.

**The Reasons Why Dyssynchrony Determined by Echocardiography Can Not Predict CRT Responder Patients**

First, reduced cardiac function depends on reduced contractility and dyssynchrony. The balance of reduced contractility and dyssynchrony is different in each patient. Pacing, even biventricular pacing, might reduce contractility of the heart muscle. CRT only improves dyssynchrony in patients with heart failure. If the disadvantage of cardiac pacing is greater than the advantage of improving dyssynchrony, the patient might be a non-responder for CRT. However, the advantage of improving dyssynchrony is greater than the disadvantage of cardiac pacing, the patient might be a non-responder for CRT. Effects of CRT depend on the balance of advantage of improving dyssynchrony and disadvantage of cardiac pacing. CRT is not always effective, even in patients with dysynchrony. Some patients with dyssynchrony have a severe case and cardiac function can not be improved, even by CRT. In the other patients with dysynchrony, cardiac function can not be improved by CRT due to non-optimal pacing site or disadvantage of cardiac pacing. Dyssynchrony and reduced contractility influences each other. Sometimes, contractility is misjudged as good due to severe dyssynchrony. Optimization of CRT setting is also a great problem. CRT does not work correctly if the CRT setting is not optimized. The CRT responder can not be predicted by dissynchrony alone.

Second, there are limitations of the methodology. Patients without dissynchrony should not be a CRT responder. However, approximately 60% of patients in whom dissynchrony can not be detected by echocardiography are CRT responders in the PROSPECT study. Although the responder rate is approximately 70% even using echocardiography, surprisingly, 60% of patients might be rejected for CRT due to absence of dyssynchrony estimated by echocardiography. The results of the DESIRE study might be reasonable. However, 42% of patients with relatively narrow QRS and without disynchrony are CRT responder. Again, these results are not acceptable.

Patients with dyssynchrony are not always CRT responder; however, patients without dyssynchrony should be CRT non-responder. Not a small percentage of patients with absence of dyssynchrony estimated by echocardiography are CRT responders. This is a very great problem. Many patients might be rejected for CRT due to absence of dyssynchrony estimated by echocardiography. If the prognosis of heart failure is good, it might be accepted. However, prognosis of heart failure is very poor. What else then CRT can we do for patients with NYHA III/IV heart failure despite the optimal medical therapy? Dyssynchrony estimated by echocardiography should not be used for patient’s selection of CRT.

**What Is the CRT Responder Rate?**

In terms of CRT responder rate, golden standard is not test outcome but the result of CRT. If the test outcome is negative, CRT is not performed. Thus, the non-responder rate is not sensitivity nor specificity. The responder rate is positive predictive value. Furthermore, sensitivity and specificity are influenced not only by the power of the test but also by the prevalence of CRT responder in the group. Absolute numbers of true-positive and false-negative are determined by the prevalence of CRT responder in the candidate group that is usually pre-selected by QRS criteria. True powers of the
Assessment of mechanical dyssynchrony is necessary in determining CRT indication until the new methods, by which CRT responder can be predicted without increasing false-negative patients, are developed in the future.

### Conclusion

At present, assessment of mechanical dyssynchrony is not necessary in determining CRT indication. Current indication including QRS width is recommended as selection criteria to identify patients suitable for CRT.

### References


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#### Table: Test outcome

<table>
<thead>
<tr>
<th>Test outcome</th>
<th>Condition determined by the golden standard=clinical results</th>
<th>Responder</th>
<th>Non-responder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>True</td>
<td>70 patients</td>
<td>30 patients</td>
</tr>
<tr>
<td></td>
<td>False</td>
<td>50 patients</td>
<td>10 patients</td>
</tr>
<tr>
<td>Negative</td>
<td>True</td>
<td>20 patients</td>
<td>20 patients</td>
</tr>
<tr>
<td></td>
<td>False</td>
<td>20 patients</td>
<td>30 patients</td>
</tr>
</tbody>
</table>

**Figure 3.** One possible example to increase the responder rate. When 100 patients are selected by the conventional electrocardiogram (ECG) criteria, there might be 70 responder patients and 30 non-responder patients. If there are 50 true-positive patients, 10 false-positive patients, 20 false-negative (potential responder) patients and 20 true-negative patients after the additional tests, the responder rate is 83% and sensitivity is 71%. The responder rate increases from 70 to 83%. However, CRT has not been done in 20 out of the 70 responder patients in this situation. No one can recognize the miserable situation, as CRT is not performed in the test-negative patients.

Echocardiographic examinations for CRT patient’s selection can be estimated in the population that is not pre-selected by the ECG criteria (Figure 1). If the number of false-positive (non-responder) patients are decreased by the additional tests in the pre-selected group (prevalence of the responder is approximately 70%), positive predictive value (=responder rate) is increased. However, the number of the true-positive (=manifest CRT responder) patients are decreased and the number of the false-negative (potential CRT responder) patients are increased in some situations if the additional tests are poor (Figure 2). One possible example is shown in Figure 3. When 100 patients are selected by the conventional ECG criteria, there might be 70 responder patients and 30 non-responder patients. If there are 50 true-positive patients, 10 false-positive patients, 20 false-negative (potential responder) patients and 20 true-negative patients after the additional tests, the responder rate is 83% and sensitivity is 71%. Responder rate increases from 70 to 83%. However, CRT is not done in 20 out of the 70 responder patients in this situation. No one can recognize the poor outcome situation, as CRT is not performed in the test-negative patients. (Figure 3).

QRS duration is used as the marker of dyssynchrony. However, QRS duration gives us the information of not only dyssynchrony but also of mixture of dyssynchrony and myocardial damages. Of course, QRS duration is not perfect for CRT patients selection. Approximately 70% of heart failure patients with prolonged QRS duration and with reduced ejection fraction can respond to CRT. QRS criteria of CRT indication might be enough for identifying patients suitable for CRT now. Efforts to increase CRT responder rate might result in increasing false-negative patients and exclude the potential CRT responder. Assessment of mechanical dyssynchrony is not necessary, rather harmful in determining CRT indication until the new methods, by which CRT responder can be predicted without increasing false-negative patients, are developed in the future.
24. Yu CM, Fung JW, Zhang Q, Chan CK, Chan YS, Lin H, et al. Tissue Doppler imaging is superior to strain imaging and post-systolic shortening on the prediction of reverse remodeling in both ischemic and non-ischemic heart failure after cardiac resynchron-
Authors’ Comments on the Pro-Side Author

After the results of several studies including PROSPECT, it is not recommended in a report from American Society of Echocardiography dyssynchrony writing group endorsed by the Heart Rhythm Society that patients who meet accepted criteria for CRT should have therapy withheld because of the results of an echocardiograph Doppler dyssynchrony study. It is advised that the dyssynchrony reporting should not include a recommendation whether a patient should undergo CRT, as this should be a clinical decision on a case-by-case basis for these borderline or challenging cases.39 Dr Kanzaki32 shows us promising new methods for detecting mechanical dyssynchrony. Unfortunately, there is no evidence of their superiorities to the conventional ECG criteria for CRT patient’s selection, which is determined by the multicenter, randomized, double blind, prospective studies. As Dr Kanzaki mentions, there are several levels of dyssynchrony including AV dyssynchrony, interventricular dyssynchrony and intraventricular dyssynchrony. There are other levels of dyssynchrony than the intraventricular dyssynchrony. Assessment of intraventricular dyssynchrony alone is not enough for CRT indication. Moreover, CRT is not always effective even in patients with dyssynchrony. Effects of CRT depend on the balance of advantage of improving dyssynchrony and disadvantage of cardiac pacing. Response for CRT can not be predicted by detecting mechanical dyssynchrony alone. At present, current indication including QRS width is recommended as selection criteria to identify patients suitable for CRT.