Absence of left ventricular apical rocking and atrial-ventricular dyssynchrony predicts non-response to cardiac resynchronization therapy

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Aims

Current imaging techniques attempt to identify responders to cardiac resynchronization therapy (CRT). However, because CRT response may depend upon several factors, it may be clinically more useful to identify patients for whom CRT would not be beneficial even under optimal conditions. We aimed to determine the negative predictive value of a composite echocardiographic index evaluating atrial-ventricular dyssynchrony (AV-DYS) and intraventricular dyssynchrony.

Methods and results

Subjects with standard indications for CRT underwent echocardiography before and during the month following device implantation. AV-DYS was defined as a percentage of left ventricular (LV) filling time over the cardiac cycle. AV-DYS, which produces a characteristic rocking of the LV apex, was quantified as the percentage of the cardiac cycle over which tissue Doppler-derived displacement curves of the septal and lateral walls showed discordance. CRT responder status was determined based on the early haemodynamic response to CRT (intra-individual improvement >25% in the Doppler-derived LV dP/dt).

Among 40 patients, optimal cut-points predicting CRT response were 31% for LV apical rocking and 39% for AV-DYS. The presence of either apical rocking >31% or AV-DYS ≤39% had a sensitivity of 95%, specificity of 80%, positive predictive value of 83%, and a negative predictive value of 94% for CRT response.

Conclusion

After pre-selection of candidates for CRT by QRS duration, application of a simple composite echocardiographic index may exclude patients who would be non-responders to CRT and thus improve the global rate of therapy success.

Keywords

Heart failure • Echocardiography • Pacing • Mechanics • CRT

Introduction

Cardiac resynchronization therapy (CRT) has proven effective in the treatment of severe heart failure, improving symptoms and quality of life1,2 as well as prognosis3 in a majority of treated patients. Unfortunately CRT is ineffective in 25–35%4 of patients and in some cases can worsen symptoms. Although current guidelines include prolonged QRS duration (>120 ms) as a criterion for selecting suitable cases for CRT, many patients with prolonged QRS intervals do not actually have mechanical dyssynchrony and fail to respond to CRT. As a result, several indices based on non-invasive imaging techniques5–9 have been developed to identify

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patients who will respond to the therapy. Unfortunately, indices of mechanical dyssynchrony (DYS) have performed poorly in larger clinical trials, showing high inter-observer variability in their measurement and failing to accurately segregate responders and non-responders to CRT. Since there is no gold standard measurement for DYS, sensitivity and specificity of criteria are based on response to therapy, which can be affected by lead placement, presence of scar, and other confounding factors that are independent of baseline DYS.

Previous echocardiographic studies have reported that intraventricular DYS produces a characteristic rocking of the apex due to the unopposed early contraction of either the septum or lateral wall of the left ventricle (LV) followed by delayed (relatively unopposed) contraction of the contralateral wall. More prominent rocking may imply active contraction as opposed to passive recoil and hence viability of the late contracting wall. The presence of this rocking motion could predict LV reverse remodelling after CRT. In addition to intraventricular DYS, abnormal atrial-ventricular (AV) synchrony can impair LV filling, contribute further to LV dysfunction, and is corrected by CRT.

The objective of this study was to determine what would be the additional value of an echocardiographic strategy using a combined index including both apical rocking and AV dyssynchrony on screening future non-responders among guidelines selected candidates (high negative predictive accuracy).

Methods

Subjects

Echocardiograms with good image quality from 53 consecutive candidates for CRT in sinus rhythm meeting current selection criteria for CRT were reviewed, regardless of previous right ventricle (RV) pacing. The aetiology of cardiomyopathy was defined according to the classification of Felker et al. Patients were classified as having ischaemic cardiomyopathy if they had one of the following: history of myocardial infarction or revascularization; ≥75% stenosis of left main or proximal left anterior descending artery; or ≥75% stenosis of two or more epicardial vessels. CRT devices were implanted transvenously with the LV lead placed in a branch of the coronary venous tree at a site that produced an acceptable pacing threshold without diaphragmatic pacing. The RV lead was positioned in the RV apex or apico-septal region. All patients received biventricular pacing and AV-delay optimization was performed within 48 h following implantation using the iterative method. A minimum of 92% biventricular pacing was sought to maximize the benefit of the therapy. The study was approved by the Massachusetts General Hospital review board for studies involving human subjects.

Routine echocardiographic measures

Doppler-echocardiography was performed using either a General Electric Vivid 7 (General Electric, Milwaukee, WI, USA) or an iE33 cardiac ultrasound machine (Philips Medical Systems, Andover, MA, USA). Subjects were examined in the left lateral recumbent position using standard views. The imaging sector was adjusted to maximize the tissue Doppler imaging frame rate (>140 frames/s). A minimum of three cardiac cycles was acquired in each recorded view. Two-dimensional- and colour-Doppler images were analysed offline using commercially available software (Echopac System, General Electric or Qlab, Philips Medical Systems). LV volumes and ejection fraction (LVEF) were calculated from the apical two- and four-chamber views using the modified biplane Simpson’s technique. LV dP/dt (mmHg/s) was measured from continuous-flow Doppler velocity profiles of the mitral regurgitant jet (MR) obtained from an apical four-chamber view, as previously described. The severity of mitral regurgitation was estimated using the proximal isovelocity surface area method.

Development of a simple method for apical rocking quantification

In normal subjects, all the walls of the LV move in a homogeneous fashion towards or away from the apex depending on the phase of the cardiac cycle (systole vs. diastole). Integration of longitudinal myocardial velocities over the cardiac cycle allows assessment of local myocardial displacement. By definition, longitudinal displacement of any segment towards the apex will appear positive (Figure 1), the ‘O’ reference point being defined at the onset of the QRS complex. In contrast, in patients with dyssynchrony, early activation of one wall, without the corresponding contraction of the contralateral wall, results in the early contracting wall moving away from the original position of the apex while the non-late-contracting wall is pulled towards this position. When this happens the displacement of the initially contracting wall will be negative (away from the apex) while the non-contracting wall will be positive (towards the apex) creating the first phase of the rocking motion (Figure 2, arrow 1). Once the late contracting wall is finally activated, it will pull the wall which contracted initially in the opposite direction, creating the second phase of this rocking motion (Figure 2, arrow 2, Supplementary data online, Video 1). The degree of LV rocking can be then simply estimated using these displacement curves from the tissue Doppler velocity recording. In practice, in a four-chamber view, a region of interest (height 10 mm × width 5 mm) was positioned at the apical end of the middle segment of the lateral and septal walls. Such positioning allows for adequate alignment of the wall with the ultrasound beam. Displacement curves were exported to a MatLab (MATLAB r2009, the MathWorks, Natick MA, USA) script. The severity of the rocking motion was defined as a per cent of the cardiac cycle during which the displacement curves were discordant (Figure 2, yellow arrows).

Quantification of atrial-ventricular dyssynchrony

Atrial-ventricular dyssynchrony (AV-DYS) was estimated by the LV filling time (measured by pulsed wave Doppler at the mitral valve leaflets) expressed as a per cent of RR interval.

Prediction of acute response to cardiac resynchronization therapy

Response to CRT was defined as the percentage change in echocardiographic-derived $\Delta \text{dP/dt}$ after 1 month of CRT. Early responders to CRT were defined as having $\Delta \text{dP/dt} >25\%$; non-responders had $\Delta \text{dP/dt} \leq 25\%$. We previously showed that the 25% threshold is highly predictive of long-term clinical outcome.

Prediction of long-term clinical outcome

Follow-up information was obtained by reviewing hospital and outpatient records. The clinical endpoints evaluated included all-cause mortality and hospitalization for worsening heart failure. These events were determined by a physician blinded to the echocardiographic results.
Inter- and intra-observer variability

For apical rocking, intra- and inter-observer variability was tested in 20 randomly selected patients by two observers blinded to other measures. Intra-class correlation coefficients for this parameter were 0.92 and 0.87, respectively.

For dP/dt, intra- and inter-observer variability in our laboratory is 0.95 and 0.91, respectively, as previously reported.26

Figure 1  Normal longitudinal displacement of lateral (yellow curve) and septal (blue curve) wall towards the apex (upslope) during systole and away from the apex (downslope) during diastole.

Figure 2  Example of left ventricular apical rocking: the displacement of the initially contracting wall (septal wall) is negative (arrow 1, away from the apex) while the non-contracting wall (lateral wall) is positive (towards the apex) in the first phase of the rocking motion. Once the delayed lateral wall is finally activated, it pulls the septum towards the apex creating the second phase of the rocking motion (Arrow 2). Yellow arrows measure the duration of the rocking motion. This duration is taken as a per cent of the cardiac cycle during which the displacement curves are discordant, almost 100% in this example.
Statistical analysis

For the comparison of parametric variables before and after CRT, the paired-sample t test was used. The impact of the underlying cardiomyopathy and the lead position was performed using ANOVA for repeated measures. Receiver operating characteristics were analysed for rocking and AV-DYS parameters. Kaplan–Meier analysis was performed for long-term outcome. All data are expressed as mean ± standard deviation. A probability value of P ≤ 0.05 was considered statistically significant. Analyses were performed using Statview 5.0 (SAS institute).

Results

Heart failure population

After exclusion of 13 patients because of insufficient mitral regurgitation for dP/dt assessment, the study group consisted of 40 patients: age 66 ± 14 years; ejection fraction 27 ± 6%; QRS 168 ± 25 ms. Twenty-two had ischaemic cardiomyopathy. All patients had a left bundle branch block pattern. Baseline characteristics are summarized in Table 1. There was no significant difference in these parameters between the ischaemic and non-ischaemic groups. Implantation lead location was lateral (38%), postero-lateral (34%), and antero-lateral (28%). Both AV dyssynchrony and LV apical rocking had a normal distribution. At baseline, average LV filling time was 49 ± 8%, ranging from 30 to 64%. Apical rocking was 39 ± 29%, ranging from 1 to 99%. There was no correlation between QRS duration and apical rocking at baseline (r² = 0.01) even after dividing the patients into two groups (ischaemic vs. non-ischaemic).

Response to cardiac resynchronization therapy and definition of optimal cut-off values for apical rocking and atrial-ventricular dyssynchrony

There was a significant overall increase in dP/dt from 586 ± 188 to 768 ± 255 mmHg (P < 0.0001) after CRT. Twenty patients had a >25% increase in dP/dt from baseline and thus were considered to be responders. The magnitude of response was independent of the underlying cardiomyopathy and of lead position. Measurement of either apical rocking or AV-DYS after CRT was technically not feasible in four patients after CRT. Although no significant changes in rocking or AV-DYS were observed in non-responders, apical rocking was reduced from 50 ± 25 to 31 ± 26% (P = 0.02) and AV-DYS slightly improved from 46 ± 9 to 50 ± 9% (P = 0.05) among responders (Figure 3). Figure 4 shows an example of patient with correction of LV apical rocking by CRT. Change in rocking was not different between the ischaemic and non-ischaemic groups.

For LV apical rocking, an optimal cut-off value of >31% was found to be predictive of a significant improvement in dP/dt with a sensitivity of 75% and a specificity of 80% (area under the curve, 0.753; confidence interval, 0.591–0.875; Figure 5A). For AV-DYS, an optimal value of ≤39% was predictive of a significant improvement in dP/dt with a sensitivity of 40% and a specificity of 100% (area under the curve, 0.690; confidence interval, 0.524–0.860; Figure 5B).

Distribution of significant apical rocking and atrial-ventricular dyssynchrony in our population

Using the cut-offs defined above, presence of either apical rocking or AV-DYS or both was found in 23 patients at baseline. Nineteen had significant apical rocking and eight had significant AV-DYS; four patients had both. Table 2 shows the distribution of the patients with respect to their baseline dyssynchrony and their response to CRT. Positive and negative predictive values of apical rocking for response to CRT were, respectively, 79 and 76% (sensitivity of 75% and specificity of 80%), whereas for AV-DYS they were, respectively, 100 and 63% with a sensitivity of 40% and a specificity of 100%. Combining both parameters (presence of either apical rocking >31% or AV-DYS ≤39%) highly improved the sensitivity (95%) with low impact on specificity (80%). The negative predictive value of this composite index was 94%, whereas the positive predictive value was only 83%.

Long-term predictive value for clinical outcome

We investigated the performance of the composite index in predicting clinical events in this population. Among the 40 patients, these data were not available in 2 patients. There was a trend for a better long-term outcome in the non-ischaemic group at
12 months ($P = 0.09$). Given the high negative predictive value of the composite index, absence of both apical rocking and AV-DYS at baseline or no correction of at least one of these parameters despite CRT was associated with a worse prognosis at 12 months, as shown by a Kaplan–Meier analysis ($P = 0.01$, Figure 6). Among the nine patients (seven ischaemic, two non-ischaemic) with clinical events, five had no apical rocking at baseline, and four had no improvement in apical rocking after CRT.

**Discussion**

This study proves the concept that an echocardiographic strategy using a combined index including both apical rocking and AV dysynchrony has value for identifying future non-responders among guidelines-selected candidates before implantation.

CRT seeks to correct mechanical DYS in patients with advanced LV failure and improve both LV function and quality of life. Intuitively, techniques that directly measure mechanical DYS as...
opposed to electrical delay should be ideal approaches to define candidates for CRT. A number of small single-centre studies using a variety of echo-Doppler techniques defined criteria for DYS based on their relationship to response to CRT. These methods in general rely on a comparison of the timing of contraction between individual segments or the difference within groups of segments in the ventricle. Unfortunately, the initial promise of these methods has not been confirmed in a subsequent multicentre trial which raises concerns about the reliability of the methods and the variability of the individual measurements. Rocking of the LV apex has been observed in patients with DYS and this rocking motion is felt to represent initial unopposed contraction of one wall (typically the septum) followed by delayed contraction of the opposite wall at a time when the early contacting wall is relaxing, thus representing intraventricular dyssynchrony more globally. Initial qualitative studies have suggested that visually detectable apical rocking indicates mechanical DYS and could predict response to CRT. Quantification of

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**Table 2** Distribution of patients with respect to their baseline level of dyssynchrony and their response to CRT

<table>
<thead>
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<th>Apical rocking ≤31%</th>
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<td></td>
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</tr>
<tr>
<td>Responders</td>
<td>Yes</td>
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</tr>
<tr>
<td></td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Non-responders</td>
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<td>20</td>
</tr>
<tr>
<td></td>
<td>Apical rocking &gt;31%</td>
<td>Apical rocking ≤31%</td>
</tr>
<tr>
<td></td>
<td>or AV-DYS ≤ 39%</td>
<td>and AV-DYS &gt; 39%</td>
</tr>
<tr>
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Distribution of patients with respect to their baseline level of dyssynchrony and their response to CRT (AV-DYS, atrial-ventricular dyssynchrony; n, number of patients).

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**Figure 5** Receiver operating characteristics for identification of early haemodynamic response to cardiac resynchronization therapy. Area under curve is provided for each graph.

**Figure 6** Comparison of long-term clinical outcome between patients with baseline apical rocking or atrial-ventricular dyssynchrony normalized by cardiac resynchronization therapy (group 1) vs. patients with either no apical rocking and atrial-ventricular dyssynchrony at baseline or no complete correction of at least one of these parameters despite cardiac resynchronization therapy (group 2); E, total number of events during follow-up, N, number of patients.
this apical longitudinal rotation using speckle tracking was shown to be a moderately strong predictor of response to CRT. Although prior methods for measuring the amount of rocking were based on the amplitude of displacement, the method utilized in this study was based on the time duration in which the two ventricular walls are moving in opposite directions, as assessed by tissue Doppler. We chose time instead of amplitude because we found measurement of the magnitude of displacement to be highly variable with small changes in the position of Doppler sampling. In addition, our approach more appropriately models the temporal disorder generated by delayed activation. We used colour tissue Doppler imaging as opposed to speckle tracking because its high frame rate allowed for a more reliable signal especially at the apical level within these enlarged ventricles. Among the different tissue Doppler modalities available, we chose to use displacement rather than velocity information since the former, which is calculated from the integration of velocity information over time, is less subject to noise. Strain information could have allowed us to distinguish between active deformation and passive motion. However, reliable signals were not possible in the apical region, where rocking is most prominent. In our initial attempts to quantify rocking, we considered including measurements from the apical two- and three-chamber views. However, we found that the axis of the LV was rarely well-aligned with the ultrasound beam (because of scanning constraints to achieve adequate visualization of the anterior wall) and that rocking is most likely to occur between the septal and lateral walls. For these reasons, we continued the development of our index using only the apical four-chamber view.

Performance of the rocking index
The simple rocking index developed here had good inter- and intra-observer variability. Using an optimal cut-off value of >31%, rocking was present in 45% of our patients. This value is lower than generally reported for mechanical dyssynchrony in this population but is not unexpected for a measure more reflective of global dyssynchrony as opposed to the maximal difference in time of contraction between two points on the opposite walls. Rocking was found to predict a significant improvement in dP/dt with a sensitivity of 75% and a specificity of 80%, and a decrease in rocking was noted only in responders to CRT. Compared with previously proposed echocardiographic indices, our rocking index alone did not show significant added value in prediction of response to CRT.

AV dyssynchrony
AV dyssynchrony, which applies only in sinus rhythm, represents a prolongation of the time between the end of atrial systole and the onset of ventricular systole, resulting in an abbreviated ventricular filling time relative to the cardiac cycle. AV dyssynchrony is often seen in conjunction with a disorder of atrioventricular conduction or QRS prolongation. Interestingly, we found a cut-off of 39% for AV-DYS, nearly identical to the value empirically chosen by Cazeau et al. (<40%). Despite its high specificity in our study (100%), AV-DYS ≤39% was present in only 20% patients explaining the low sensitivity of this test (62.5%). Dual chamber pacing, by linking ventricular to atrial activation, normalizes ventricular filling. In fact, DDD pacing was proposed as a potential treatment of refractory heart failure but this approach was limited by the intra-ventricular dyssynchrony created by RV pacing. However, improvement of LV filling by optimal AV pacing is still considered as an important determinant of response to CRT and change in AV delay is the only parameter considered for optimization by current guidelines.

A combined echocardiographic index
Since mechanical dyssynchrony impacts both diastole and systole, we chose to combine our measures of intraventricular dyssynchrony and AV dyssynchrony into a DYS index. Combining both parameters (presence of either apical rocking >31% and/or AV-DYS ≤39%) improved the sensitivity for detection of a positive response to CRT with little impact on specificity reflecting the fact that roughly 20% of patients who failed to meet these criteria still responded to CRT (positive predictive value 83%). Significantly, however, the negative predictive value of this composite index was 94% with only one patient who failed to meet either of these criteria responding to CRT. Thus, as expected, since prediction of positive response to CRT is influenced by many confounding factors such as lead placement or presence of scar, we were not able to demonstrate a significantly higher positive predictive value than previously published parameters. However, with a high negative predictive value, this echocardiographic strategy could differ from previous ones by its ability to identify patients who will not respond to the therapy, even if implantation is
considered to be optimal. These results were reinforced by long-term follow-up since absence of baseline dyssynchrony as defined in our study or its persistence despite CRT was associated with worse prognosis. Our results may thus be applied in the following strategy (Figure 7): a patient who meets the usual criteria for CRT undergoes an echocardiogram before implantation. If either AV-DYS is ≤39% OR apical rocking is >31% then the patient is considered as having at least one level of mechanical dyssynchrony and may respond to CRT following optimal device implantation. In such a case, the patient could be further evaluated by additional techniques to evaluate for scar tissue or improve lead implantation. However, if LV filling is >39% AND apical rocking is ≤31% then it is highly probable that this patient will be a non-responder.

**Limitations**

Our study has several limitations. First, our new index is only applicable to patients in sinus rhythm. Second, LV rocking could not be measured in 13% of the patients meeting criteria for this study because of poor image quality. Third, one responder in our cohort would have been inappropriately excluded from CRT if our screening strategy had been applied, such that our negative predictive value was not equal to 100%. Despite reviewing pre- and post-implant echocardiograms in this patient, we were not able to understand what the mechanism of response was in this specific patient, whose early haemodynamic response was confirmed clinically after a follow-up of 1 year with no events.

In addition, our analysis of early response to CRT was confined to patients with sufficient MR to accurately measure dP/dt. Therefore, it is possible that patients without significant MR, especially after resynchronization, may have a different acute hemodynamic response to CRT compared with the 40 patients in this study. However, while MR was necessary for assessment of response in this study, our index may perform similarly in patients without MR, a hypothesis which will need confirmation using an alternative standard for response. In this cohort, dP/dt was measured within the first month following the implantation, thereby reducing the impact of time, remodelling, or any other confounding variable on cardiac performance.

AV optimizations were performed within 48 h following the implantation. It is possible that routine post-procedural AV optimizations could have impacted the results of this study. LV lead position was considered optimal based on EP criteria (suitable anatomical position at a site with acceptable pacing threshold but no diaphragmatic pacing) without consideration of viability or identification of the latest activated LV segment. Unlike previous work where the extent of reduction in LV end-systolic volume at 3–6 months was most predictive of long-term outcome, we could not examine the impact on reverse remodelling as a large number of our patients were not followed in our centre. However individual cases show significant reduction in end-systolic volume associated with correction of dyssynchrony (Supplementary data online, Video 2). Finally, our results are based on a limited number of patients and the cut-off values we identified for apical rocking and AV-DYS were applied to the population in which they were developed and not in a different population which may have overestimate the performance of our strategy.

**Conclusion**

Although most studies focus on the ability to identify responders to CRT, we propose that it may be more clinically appropriate to identify non-responders to CRT. This would prevent the risks of inappropriate pacing and improve the overall rate of therapy success. We show how a simple echocardiographic strategy incorporating AV and intra-ventricular dyssynchrony, in conjunction with the usual guidelines for CRT, could successfully identify patients in whom the procedure may not be beneficial and in whom implantation, with its attendant risks, may be avoided. However, this concept should be validated in a much larger group of patients with a multicentre blinded study.

**Supplementary data**

Supplementary data are available at European Journal of Echocardiography online.

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