CHAPTER 3

Real-time three-dimensional echocardiography permits quantification of left ventricular mechanical dyssynchrony and predicts acute response to cardiac resynchronization therapy

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ABSTRACT

Objectives: To evaluate the value of real-time 3-dimensional echocardiography (RT3DE) to predict acute response to cardiac resynchronization therapy (CRT).

Methods: 60 consecutive heart failure patients scheduled for CRT were included. RT3DE was performed before and within 48 hours after pacemaker implantation to calculate both left ventricular (LV) volumes and LV dyssynchrony. LV dyssynchrony was defined as the standard deviation of the time taken to reach the minimum systolic volume for 16 LV segments (referred to as the systolic dyssynchrony index, SDI). Patients were subsequently divided into acute responders or non-responders, based on a reduction ≥15% in LV end-systolic volume immediately after CRT.

Results: 4 patients (7%) were excluded from further analysis because either suboptimal apical acquisitions or significant translation artefacts. Out of the remaining 56 patients, 35 patients (63%) were classified as acute responders. Baseline characteristics were similar between responders and non-responders, except for the SDI, which was larger in responders. Moreover, responders demonstrated a significant reduction of SDI immediately after CRT (from 9.7±4.1% to 3.6±1.8%, p <0.001), whereas SDI did not change in non-responders (3.4±1.8% versus 3.1±1.1%, NS). ROC curve analysis revealed that a cut-off value for SDI of 5.6% yielded a sensitivity of 88% with a specificity of 86% to predict acute echocardiographic response to CRT (AUC 0.96).

Conclusions: RT3DE is highly predictive for acute response to CRT (sensitivity 88% and specificity 86%). In addition, RT3DE allows assessment of changes in LV volumes and LV ejection fraction before and after CRT implantation.
INTRODUCTION

In recent years cardiac resynchronization therapy (CRT) has become an established therapy for patients with drug-refractory heart failure and a wide QRS complex. However, close analysis of the large CRT trials revealed that up to 30% of patients did not respond to CRT when the established selection criteria were applied. Several studies addressing this issue have indicated that the presence of baseline left ventricular (LV) dyssynchrony is an important predictor of response to CRT. In the established selection criteria, the presence of a wide QRS complex has been used as a marker of cardiac dyssynchrony; however, recent findings showed that QRS duration correlated poorly with LV dyssynchrony, thereby explaining its poor predictive value for response to CRT. Conversely, direct echocardiographic assessment of LV dyssynchrony has been demonstrated highly predictive for response to CRT. Since this observation, various echocardiographic parameters have been proposed to appropriately select CRT candidates ranging from simple M-mode-echocardiography to more advanced techniques such as tissue Doppler imaging (TDI).

Recently, real-time 3-dimensional echocardiography (RT3DE) has become available as a novel promising technique for assessment of LV dyssynchrony based on analysis of regional volumetric changes of the LV. A potential advantage of the use of RT3DE in patients undergoing CRT is that it allows both LV dyssynchrony assessment as well as highly accurate three-dimensional quantification of LV volumes and LV function during follow-up which allows assessment of therapy success. An initial study by Kapetenakis et al. demonstrated promising results when RT3DE was applied in a small group of patients undergoing CRT. In the current study, the value of RT3DE for prediction of response to CRT and the assessment LV volumes following CRT implantation was evaluated in a larger group of patients undergoing CRT implantation.

METHODS

Patient population and protocol

Sixty consecutive heart failure patients, scheduled for implantation of a CRT device, were included in this study. Patients were selected for CRT on the following basis:
- LV ejection fraction (EF) ≤35%,
- QRS duration >120 ms and
- NYHA functional class III or IV, despite optimal medical treatment.
Etiology was considered ischemic in the presence of significant coronary artery disease (>50% stenosis in ≥1 major epicardial coronary artery) on coronary angiographic examination and/or a history of myocardial infarction and previous coronary artery revascularizations. Patients with a recent myocardial infarction (<3 months) or decompensated heart failure were excluded.

Before implantation of the CRT device, LV volumes, LVEF and LV dyssynchrony were measured using RT3DE. LV stroke volume (SV) was also calculated using the pulsed-wave Doppler signal in the LV outflow tract. All echocardiographic measurements were repeated immediately (within 48 hours) after CRT implantation and the analysis was performed blinded to the pre-implantation data.

In addition, 20 patients were randomly identified to evaluate the inter- and intra-observer agreement for the analysis of LV volumes, LVEF and dyssynchrony. Bland-Altman analysis was performed to evaluate agreement between observer 1 and observer 2 to assess inter-observer agreement and between 2 measurements by observer 1 to assess intra-observer agreement.

Real-time 3-dimensional echocardiography

Acquisition of 3-dimensional data set

RT3DE was performed before and within 48 hours after CRT implantation. Patients were imaged in the left lateral decubitus position with a commercially available system (IE33, Philips Medical Systems, N.A., Bothell, Washington, USA) equipped with X3, fully sampled matrix transducer. Apical full-volume data sets were obtained in all patients.

For the evaluation of LV volumes and LVEF, the lowest scan line density was used and gain and compression were adjusted to obtain a good image quality and a clear endocardial border. With a specific software (Large Volume size, Vision 2007, Philips Medical Systems) 4 small real-time sub-volumes were acquired from alternate cardiac cycles and combined to provide a larger pyramidal volume (up to 103 x 103 degrees) and to ensure a complete capture of the LV. The acquisition was performed during end-expiratory apnoea within 1 breath hold and with a relatively stable heart rate to minimize translation artefacts between the 4 sub-volumes. A 3D data set was considered unsuitable for analysis if >2 segments could not be visualized or if it contained visible translation artefacts. For the evaluation of LV dyssynchrony the frame rate was optimized by reducing the depth and by the acquisition of a full-volume data set of 7 sub-volumes.
LV volumes and LV ejection fraction

RT3DE data sets were stored digitally and quantitative analysis of the 3D dataset was performed off-line using a semi-automated contour tracing algorithm (Q-Lab, version 5.0, Philips Medical Systems) over a complete heart cycle. The software provides for each frame the apical 4 chamber and 2 chamber views and the parasternal short-axis view. After first identifying the apex and mitral annulus on the end-diastolic and end-systolic frames (using 5 reference points), a preconfigured ellipse is fitted to the endocardial border for each frame (mean number of frames: 16±4) and manually adjusted as required. The three-dimensional model of the LV is generated and LV volumes and LVEF are obtained (Figure 1). Papillary muscles were included in the LV cavity. The post-processing of the images required between 2 and 4 minutes, depending on the manual adjustments needed.

Patients with an acute reduction ≥15% of LV end-systolic volume (reflecting acute improvement in LV systolic function) were considered acute responders to CRT. Additionally, LV SV was calculated before and within 48 hours after pacemaker implantation, using the pulsed-wave Doppler signal in the LV outflow tract from the apical long-axis view.

![Figure 1](image_url)

**Figure 1.** Example of 3D left ventricular (LV) volumes generated by post-processing of a RT3DE dataset, acquired in a patient scheduled for CRT. Panel A: pre CRT. Panel B: immediately post CRT. LV end-systolic volume (LVEDV) and LV ejection fraction (LVEF) improved significantly.
Assessment of LV dyssynchrony

The LV 3D model was subdivided in 16 pyramidal sub-volumes (6 basal segments, 6 mid segments and 4 apical segments). For the whole LV and for each volumetric segment, it is possible to derive time-volume data for the entire cardiac cycle and assess the time taken to reach the minimum systolic volume (Tmsv). From this information, as previously described by Kapetanakis et al., the standard deviation of 16 segments Tmsv expressed in percentage of cardiac cycle (the systolic dyssynchrony index, SDI) was calculated as a marker of global dyssynchrony of the LV. Of interest, the time-volume data of an akinetic segment is displayed by the software as a flat curve (excursion = 0) and the minimum systolic volume is identified in the middle of this curve, substantially not affecting the deviation standard of the timings (SDI). A completely dyskinetic segment (positive excursion) is excluded from the SDI calculation. For the baseline SDI calculation 36 out of 896 segments (4%) were discarded because dyskinetic; 232 segments (26%) were defined akinetic. After CRT, the same number of dyskinetic segments was found, whereas the number of akinetic segments decreased to 198 (22%).

Figure 2. Example of left ventricular (LV) dyssynchrony analysis from a RT3DE data set using parametric images. The global Tmsv is used as timing reference; early segments are coded in blue, whereas late segments are coded in red. Pre CRT: Before CRT, the inferior segments are activated last. Post CRT: the homogeneous color indicates absence of regions with delayed activation, indicating resynchronization after CRT implantation. After implantation the systolic dyssynchrony index (SDI) decreased from 13.6% to 1.9%.
In addition to the time-volume data, parametric images, derived from over 800 virtual waveforms, are provided by the software (Q-Lab, version 5.0, Philips Medical Systems) with a visual summary, as a polar plot, of LV regional contraction timings. The global Tmsv is used as timing reference. Accordingly, segments with a Tmsv about global Tmsv are coded in green. Early segments are coded in blue, whereas late segments are coded in red/yellow (Figure 2). Using both analysis of the regional time-to-minimum systolic volume and the parametric images, the latest activated LV wall (either lateral, posterior, inferior, septal, anteroseptal or anterior) was identified as a marker of regional dyssynchrony.

Reproducibility of the RT3DE measurements

Twenty patients were randomly identified for inter- and intra-observer agreement. Bland-Altman analysis was performed to evaluate agreement between observer 1 and observer 2 to determine inter-observer agreement. Similarly, the 3D measurements derived by the first observer were compared (Bland-Altman analysis) with the results calculated by the same operator 1 month later to determine intra-observer agreement.

The inter-observer agreement was good. According to the Bland-Altman analysis, the mean differences for SDI, LV end-diastolic volume (EDV), end-systolic volume (ESV) and EF were 0.1±1%, 1.3±17 ml, 0.3±17 ml and 0.4±4%, respectively, all not significantly different from zero. The intra-observer agreement was also good. The agreement between the 2 measurements according to the Bland-Altman analysis was excellent with mean differences of 0.03±0.5% for SDI, 0.6±10 ml for LVEDV, 0.7±6 ml for LVESV and 0.8±3% for LVEF, all not significantly different from zero.

Pacemaker implantation

The LV pacing lead was inserted transvenously via the subclavian route. First, a coronary sinus venogram was obtained using a balloon catheter. Next, the LV pacing lead was inserted through the coronary sinus, using an 8Fr-guiding catheter, and positioned as far as possible in the venous system, preferably in the (postero-) lateral vein. The right atrial and ventricular leads were positioned conventionally. When an indication for an internal defibrillator existed, a combined device was implanted. In all patients the implantation of the CRT device was successful without major complications (Contak Renewal, Guidant Corp.; Insync III-CD or Insync Sentry, Medtronic Inc.). Two types of LV leads were used (Easytrak, Guidant Corp., or Attain, Medtronic Inc.). For each patient, the atrio-ventricular interval was adjusted to maximize mitral inflow duration with pulsed-wave Doppler echocardiography. No adjustment of the inter-ventricular delay was made.
Statistical analysis

Continuous data are presented as mean ± standard deviation. Categorical data are presented as absolute numbers or percentages. Comparisons between responders and non-responders were performed using the independent-samples \( t \)-test; comparisons between pre- and post-implantation characteristics were performed using the paired-samples \( t \)-test. Before performing a Student’s \( t \)-test, the normal distribution of the continuous variables was verified using the Kolmogorov–Smirnov test and using the Levene’s test to check for equality in variances for all comparisons. Correlation analysis was used to compare the relationship between the change of SDI and the change of LVESV, LVEF and LV SV after CRT by the Pearson correlation coefficients. Optimal cut-off value of SDI to predict acute echocardiographic response to CRT was determined by receiver-operating characteristic (ROC) curve analysis. The optimal cut-off value was defined as that providing the maximal accuracy to distinguish between echocardiographic responders/non-responders. For all tests, a \( p \)-value <0.05 was considered significant. A statistical software program SPSS 12.0 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis.

RESULTS

Patient population

The study population consisted of 60 consecutive heart failure patients. Four patients (7%) were excluded from further analysis because of suboptimal apical acquisitions or significant translation artefacts. The baseline characteristics of the remaining 56 patients (45 men, mean age 65±9 years) are summarized in Table 1. All patients were in sinus rhythm and most patients were in NYHA class III; 62% of patients had ischemic cardiomyopathy. RT3DE revealed severe LV dilation (mean LVEDV 201±48 ml), with depressed LV function (mean LVEF 28±6%). In addition, substantial LV dyssynchrony was present as indicated by a mean SDI of 7.3±4.6%. The latest activated LV wall was the lateral in 17 patients (30%), the posterior in 16 patients (29%), the inferior in 13 patients (23%), the anterior in 9 patients (16%) and the septum in 1 patient (2%).

Acute echocardiographic response

Immediately after CRT implantation, 35 patients (63%) experienced an acute reduction in LVESV ≥15%; as pre-defined, these patients were classified as acute responders. The acute responders also showed a significant increase in LVEF and LV SV (Table 2). In contrast, LVEDV showed no immediate decrease after CRT implantation (from 201±48 ml to 191±46 ml, NS) (Table 2).
Table 1. Baseline characteristics of the patient population (n = 56).

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<table>
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<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td><strong>65±9</strong></td>
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<tr>
<td>Gender (M/F)</td>
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<tr>
<td>NYHA class III/IV (n)</td>
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<td>QRS duration (ms)</td>
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<td>ECG pattern:</td>
<td></td>
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<td>LBBB/IVCD, n (%)</td>
<td>37(66)/19 (34)</td>
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<td>Etiology, n (%)</td>
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<tr>
<td>Ischemic</td>
<td>35 (62)</td>
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<tr>
<td>Idiopathic</td>
<td>21 (38)</td>
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<tr>
<td>Medication, n (%)</td>
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<td>ACE Inhibitors</td>
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<td>ß-blockers</td>
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<tr>
<td>Diuretics and /or</td>
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<tr>
<td>Spironolactone</td>
<td>53 (95)</td>
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<tr>
<td>Amiodarone</td>
<td>8 (14)</td>
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<td>LVEDV (ml)</td>
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<td>LVESV (ml)</td>
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<td>LVEF (%)</td>
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<tr>
<td>LV SV (ml)</td>
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<td>SDI (%)</td>
<td>7.3±6</td>
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Table 2. Responders versus non-responders: echocardiographic variables before and immediately after CRT implantation.

<table>
<thead>
<tr>
<th></th>
<th><strong>Non-responders</strong></th>
<th><strong>Responders</strong></th>
<th><strong>p-value</strong></th>
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<tr>
<td></td>
<td><strong>n = 21</strong></td>
<td><strong>n = 35</strong></td>
<td></td>
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<tr>
<td>LVEDV (ml) Baseline</td>
<td>202±50</td>
<td>201±48</td>
<td>NS</td>
</tr>
<tr>
<td>After implantation</td>
<td>200±49</td>
<td>191±46</td>
<td>NS</td>
</tr>
<tr>
<td>LVESV (ml) Baseline</td>
<td>148±42</td>
<td>147±44</td>
<td>NS</td>
</tr>
<tr>
<td>After implantation</td>
<td>145±41</td>
<td>124±38*</td>
<td>0.05</td>
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<tr>
<td>LVEF (%) Baseline</td>
<td>27±7</td>
<td>28±6</td>
<td>NS</td>
</tr>
<tr>
<td>After implantation</td>
<td>28±6</td>
<td>36±6*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV SV (ml) Baseline</td>
<td>37±15</td>
<td>39±13</td>
<td>NS</td>
</tr>
<tr>
<td>After implantation</td>
<td>37±14</td>
<td>47±14*</td>
<td>0.01</td>
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<tr>
<td>SDI (%) Baseline</td>
<td>3.4±1.8</td>
<td>9.7±6.1</td>
<td>NS</td>
</tr>
<tr>
<td>After implantation</td>
<td>3.1±1.1</td>
<td>3.6±1.8*</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*p <0.001 baseline versus follow-up. Abbreviations see Table 1.
Table 3. Baseline clinical characteristics of responders versus non-responders.

<table>
<thead>
<tr>
<th></th>
<th>Non-responders n = 21</th>
<th>Responders n = 35</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66±8</td>
<td>65±10</td>
<td>NS</td>
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<tr>
<td>Gender (M/F)</td>
<td>16/5</td>
<td>29/6</td>
<td>NS</td>
</tr>
<tr>
<td>Ischemic/Idiopathic (n)</td>
<td>15/6</td>
<td>20/15</td>
<td>NS</td>
</tr>
<tr>
<td>NYHA class III/IV (n)</td>
<td>21/0</td>
<td>32/3</td>
<td>NS</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>157±29</td>
<td>147±35</td>
<td>NS</td>
</tr>
<tr>
<td>ECG pattern:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LBBB/IVCD (n)</td>
<td>9/12</td>
<td>10/25</td>
<td>NS</td>
</tr>
</tbody>
</table>


All baseline characteristics were comparable between responders and non-responders, except for LV dyssynchrony as measured with the use of RT3DE (assessing SDI) (Table 2 and Table 3). The SDI was significantly higher in responders as compared to non-responders (9.7±4.1% versus 3.4±1.8%, p <0.001). Moreover, responders demonstrated a significant reduction in SDI immediately after CRT (from 9.7±4.1% to 3.6±1.8%, p <0.001), whereas in non-responders SDI remained unchanged (from 3.4±1.8% to 3.1±1.1%, NS) (Table 2). In addition, the postero-lateral region (where the LV pacing lead is positioned) was latest activated in 74% of responders as compared to 33% of non-responders (p = NS).

**Prediction of acute response after CRT implantation by RT3DE**

A fair correlation was observed between baseline SDI and the change in LVESV after CRT (r = 0.60, p <0.001), while a good correlation between baseline SDI and the change in LVEF after CRT was demonstrated (r = 0.70, p <0.001) (Figure 3). A fair correlation was also noted between baseline SDI and the change in LV SV after CRT (r = 0.51, p <0.001).

![Figure 3](image.png)

*Figure 3.* The correlation between the change (delta) in LV ejection fraction (LVEF) after CRT and baseline systolic dyssynchrony index (SDI) is shown.
To define the optimal cut-off value to predict echocardiographic response to CRT, ROC curve analysis was performed. At a cut-off value of 5.6% for LV dyssynchrony (SDI), a sensitivity of 88% with a specificity of 86% were obtained to predict an acute reduction ≥15% of LVESV (area under the curve = 0.96, 95% CI = 0.9 -1.0, p <0.001) (Figure 4). Accordingly, using

![ROC curve analysis](image)

**Figure 4.** ROC curve analysis demonstrated a sensitivity of 88% with a specificity of 86% to predict an acute reduction of left ventricular end-systolic volume ≥15% after CRT at a cut-off of 5.6% for LV dyssynchrony (SDI). AUC = area under the ROC curve.

![Comparison between patients](image)

**Figure 5.** Comparison between patients with substantial versus non-substantial LV dyssynchrony (SDI) (cut-off value of ≥5.6%). The decrease in LV end-systolic volume (Panel A) and the increase in LV ejection fraction (Panel B) and in LV stroke volume (Panel C) are significantly higher in patients with substantial LV dyssynchrony.
this cut-off value, 34 patients (61%) had SDI ≥5.6%; these patients showed a significantly better improvement in LV systolic function (defined as a reduction of LVESV and an increase in LVEF and SV) as compared to patients with SDI <5.6% (Figure 5).

DISCUSSION

The findings in the current study can be summarized as follows: 1) acquisition and analysis of a RT3DE data set is feasible and reproducible in patients with severely dilated left ventricles and provides quantitative information on both LV volumes and LV dyssynchrony; 2) all baseline characteristics were comparable between responders and non-responders to CRT, except for LV dyssynchrony as measured using the SDI, which was larger in responders; 3) a SDI ≥5.6% had a sensitivity of 88% and a specificity of 86% to predict an acute reduction in LVESV after CRT implantation.

Benefit of CRT

Recent large clinical trials have demonstrated the beneficial effects of CRT on symptoms, exercise capacity, LV reverse remodeling and, most important, on clinical outcome. However, despite these impressive results approximately one third of patients fails to improve after CRT when the established selection criteria are being applied (NYHA functional class III or IV, LVEF ≤35% and QRS duration >120 ms). Several studies have recently emphasized the importance of the presence of significant baseline LV dyssynchrony for the prediction of response to CRT. Traditionally QRS duration has been used as a marker of LV dyssynchrony; however recent data has suggested that QRS duration is a poor marker of LV dyssynchrony, thereby explaining its poor predictive value for response to CRT. Since the observation that QRS duration is a poor marker of LV dyssynchrony several echocardiographic methods have been introduced to quantify LV dyssynchrony. Most experience has been obtained with tissue Doppler imaging. For example Bax and colleagues analyzed the electromechanical activation delay in the longitudinal direction among 4 basal LV segments, whereas Yu et al. have used the standard deviation of time-to-peak systolic velocity of 12 LV segments. Both studies have identified the TDI parameters of LV dyssynchrony as powerful predictors of clinical response and LV reverse remodeling after CRT. More recently, also radial LV dys-synchrony assessed by speckle tracking strain was able to predict immediate and long-term response to CRT. At present, it is still unclear which technique is the gold standard for LV dyssynchrony since large comparative studies directly comparing the relative merits of the different techniques are lacking.
RT3DE predicts acute response to CRT

RT3DE has been recently introduced as a promising technique for the assessment of LV dysynchrony. In theory RT3DE has several potential advantages over other echocardiographic techniques: 1) Next to LV dyssynchrony analysis RT3DE permits highly accurate quantitative measurement of LV size and function which allows for simultaneous evaluation of therapy success, 2) RT3DE measures a composite effect of longitudinal, radial and circumferential contraction which is angle-independent, potentially resulting in more reproducible results and, 3) RT3DE is able to measure all (16) myocardial segments in 1 single recording allowing for a rapid assessment of the area of latest LV activation to guide optimal LV lead placement.

Assessment of LV volumes and LV function by RT3DE

A recent study by Yu et al. demonstrated that a reduction in LV end-systolic volumes is the best predictor of improved survival after CRT, whereas improvement in clinical parameters was not predictive. Therefore improvement in LV volumes after CRT implantation probably provides the most clinical meaningful marker of therapy success. Quantification of LV end-systolic volume before CRT and during follow-up is therefore crucial in order to assess therapy success. In most studies the measurement of LV volumes and LVEF has been performed with echocardiography from a 2D dataset using the Simpson’s biplane method. It has been demonstrated however, that the 3D echocardiographic approach is superior compared to the 2D approach and comparable with magnetic resonance imaging for LV volumes estimation. RT3DE, which was used in the current study, permits a rapid and accurate quantification of LV size and function with a semi-automated contour-tracing algorithm. Initial studies in CRT patients have used RT3DE to assess both acute changes in LV volumes as well as the effects at mid-term follow-up. In the current study a reduction ≥15% of LVESV immediately after CRT (reflecting improved LV systolic function) was used to define acute response and non-response after CRT. An acute improvement in LV end-systolic volume was noted in 63% of patients; this finding is in agreement with other studies focusing on the acute response to CRT using different 2D echocardiographic parameters including dP/dT, stroke volume, LVESV and LVEF.

Of interest, RT3DE can also provide information on regional LV function (measured as excursion) and consequently information on regional wall motion abnormalities. For instance, an akinetic segment is displayed as a flat curve, a dyskinetic segment as a positive excursion, whereas hypo- and normokinetic segments are displayed as negative excursions. Not only may the presence of baseline wall motion abnormalities (per se or included in wall motion score index) have influence on response to CRT, but also the effect of CRT on regional LV function can be evaluated. However, no studies have validated RT3DE (versus MRI or 2D echocardiography) for this specific analysis. Of note, wall motion abnormalities, such as akinesia and dyskinesia, do not affect the SDI calculation.
Assessment of LV dyssynchrony by RT3DE

In a small group of patients Kapetanakis and coworkers demonstrated that patients with a significant improvement in symptoms and LV reverse remodeling after CRT (responders) had a larger SDI before CRT implantation, as compared to non-responders to CRT. In the current study similar results were found in a group of 56 heart failure patients: a higher SDI value was noted in the responders as compared to non-responders (9.7±4.1% versus 3.4±1.8%, p<0.001). However, the absolute SDI values were somewhat lower in the current study. This difference may partially be explained by the different software packages used for the 3D dataset analysis. In contrast to the Tomtec-software (as used by Kapetanakis et al.), the Q-lab software (used in the current study) does not permit the operator to change the point of time-to-minimum systolic volume which is automatically detected, yielding a better reproducibility of the measurements, which tends to result in lower SDI values. Another difference between both studies is the fact that Kapetanakis et al. used an arbitrary cut-off value for significant mechanical dyssynchrony, which was defined as an SDI >3 SD above the mean for a group of normal subjects (8.3%). In the current study on the other hand, ROC curve analysis was performed to define the optimal cut-off value for SDI to predict response to CRT in a group of heart failure patients undergoing CRT; based on this ROC curve analysis, an SDI ≥5.6% was identified as the optimal cut-off value which yielded a sensitivity of 88% with a specificity of 86% to predict an acute response to CRT. In contrast, the earlier proposed value of 8.3% for SDI yielded an excellent specificity (100%) with a lower sensitivity of 46%. Burgess et al. compared RT3DE and TDI for the assessment of LV dyssynchrony. Applying a cut-off value of 32 ms for the Ts-SD of 12 segments and of 8.3% (cut-off value of Kapetanakis et al.) for the SDI, these authors demonstrated that TDI identified a much greater proportion of patients with significant LV dyssynchrony than RT3DE (64% versus 42%), suggesting that the population derived cut-off value of Kapetanakis is somewhat high.

An important advantage of RT3DE is the simultaneous assessment of 16 LV segments in 1 recording. Through the analysis of each regional time-to-minimum systolic volume and the display of parametric imaging in polar plots (Figure 2), RT3DE permits a rapid identification of the area of latest mechanical activation. Tailoring the LV lead position to the exact area of maximal mechanical delay has recently attracted attention, although the technical limitations of transvenous coronary sinus pacing still exist. Several studies demonstrated that LV pacing at the site of latest activation is associated with the maximal clinical benefit and the greatest LV reverse remodeling compared with LV pacing at the standard location (the postero-lateral wall). In line with these results, the current study showed a clear, although not statistically significant, trend of a higher percentage of patients with the postero-lateral wall as the site of latest activation in responders (74%) compared to non-responders (33%).
Study limitations

Echocardiographic or clinical data at mid- or long-term follow-up were not available and the present study focused on acute response to CRT. However, several studies, as discussed above, have already explored the acute beneficial effects of CRT and, recently, Suffoletto et al. demonstrated that acute improvement in systolic function translated in LV reverse remodeling at mid-term follow-up \(^\text{10}\). In view of the relatively small study population and the novelty of this technique, the predictive value of RT3DE needs to be further investigated in a multicenter prospective study. Also, the predictive value of RT3DE (SDI) as evaluated in the current study was not compared to other echocardiographic techniques currently available for LV dyssynchrony assessment such as TDI and strain imaging. Further multicenter studies are needed to explore the relative merits of the different techniques for the prediction of response to CRT, in order to define a gold standard for LV dyssynchrony assessment in CRT patients.

Recent studies have indicated that regional scar tissue and global scar burden may also be related to non-response to CRT. Data on scar tissue and/or segmental wall motion abnormalities, however, were not systematically available in the current study. Furthermore, no data were available on the exact position of the LV pacing lead and consequently data on the potential effect of LV lead position in relation to the site of latest activation were not available.

CONCLUSIONS

RT3DE allows quantitative analysis of LV dyssynchrony as well as assessment of LV volumes and ejection fraction in heart failure patients. An SDI $\geq 5.6\%$ is highly predictive for acute volumetric response to CRT.
REFERENCES


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