CHAPTER 6

Tri-plane tissue Doppler imaging: a novel 3-dimensional imaging modality that predicts reverse left ventricular remodeling after cardiac resynchronization therapy

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ABSTRACT

Objectives: Several 2-dimensional TDI echocardiographic techniques have proven useful to identify CRT responders. Recently a 3-dimensional probe allowing simultaneous acquisition of TDI data in 3 imaging planes became available. The present study evaluated the value of tri-plane tissue Doppler imaging (TDI) to predict reverse left ventricular (LV) remodeling after cardiac resynchronization therapy (CRT).

Methods: Sixty heart failure patients, scheduled for CRT, underwent tri-plane echocardiography with simultaneous TDI acquisition before and 6 months after implantation. From the tri-plane dataset a 3-dimensional left ventricular (LV) volume was generated and LV volumes and ejection fraction were calculated. Intraventricular dyssynchrony was quantitatively analyzed by evaluating time from onset QRS to peak myocardial systolic velocity in 12 LV segments from the tri-plane dataset and calculation of the standard deviation (Ts-SD-12). Clinical response was defined as an improvement of at least 1 New York Heart Association class. Reverse LV remodeling was defined as ≥15% decrease of LV end-systolic volume at 6 months follow-up.

Results: Responders to CRT had significantly more LV dyssynchrony at baseline than non-responders; Ts-SD-12: 42±14 versus 22±12 (P<0.0001). A cut-off value of 33 for baseline Ts-SD-12, acquired from the tri-plane TDI dataset, yielded a sensitivity of 89% with a specificity of 82% to predict clinical response to CRT; sensitivity and specificity to predict reverse LV remodeling were 90% and 83%.

Conclusions: Tri-plane TDI echocardiography predicts clinical response and reverse LV remodeling 6 months after CRT implantation.
INTRODUCTION

Cardiac resynchronization therapy (CRT) is now accepted as an alternative therapeutic option in heart failure patients who remain highly symptomatic despite optimized medical treatment \(^1\). However, using classic selection criteria for CRT including New York Heart Association (NYHA) Class III or IV, impaired left ventricular (LV) systolic function and conduction delay on the surface electrocardiogram (i.e. wide QRS complex >120 ms), up to 30% of CRT patients do not respond favourably \(^2\). The presence of LV dyssynchrony is considered a key issue in the identification of potential responders to CRT \(^3,4\). Numerous 2-dimensional (2-D) echocardiographic methods, often using tissue Doppler imaging (TDI), have been proposed to quantify LV dyssynchrony and predict response to CRT \(^5-10\). The TDI method originally described by Yu and co-workers is a standard deviation of electromechanical activation times (Ts-SD-12) based on a 12-segment model of the LV \(^7,11\). To calculate this dyssynchrony parameter, 3 different apical views need to be acquired separately, non-simultaneously, thus neglecting heart rate variability. Recently, a 3-dimensional (3D) TDI imaging modality, tri-plane TDI, became available which permits simultaneous acquisition of TDI from all LV segments during the same heartbeat. In addition, the tri-plane technique allows calculation of 3-D volumes and LV ejection fraction. There are no published data available on the potential role of tri-plane TDI to predict response to CRT.

In the present study, this novel 3-D echocardiographic technique, tri-plane TDI, was applied to 60 heart failure patients to quantify LV volumes, ejection fraction and LV dyssynchrony at baseline and at 6 months follow-up. Aim of the study was to assess the value of this tri-plane approach to predict clinical response and reverse LV remodeling, 6 months after CRT implantation.

METHODS

Patient population

The study population comprised of 60 consecutive heart failure patients scheduled for CRT. Inclusion criteria were severely symptomatic heart failure despite optimal medical treatment (NYHA class III or IV), depressed LV ejection fraction and wide QRS complex (>120 ms, with left bundle branch block or interventricular conduction delay) on the surface electrocardiogram. Patients with atrial fibrillation or a previously implanted pacemaker were excluded.
Study protocol

Within 24 hours before CRT implantation, all patients underwent the following examinations: 12-lead electrocardiogram and extensive tri-plane transthoracic echocardiography as described below. NYHA functional class was assessed by a clinician blinded to all other data. Subjects completed the Minnesota living-with-heart-failure questionnaire, a 21-question self-administered instrument with scores ranging from 0 to 5 for each question; higher scores indicate poorer quality of life. Exercise capacity was assessed using the 6-minute hall walk test. Six months after implantation of the CRT device, all patients underwent the same examinations including tri-plane echocardiography.

Tri-plane TDI echocardiography

Acquisition of the 3D dataset

Studies were performed with a commercially available echocardiographic platform (VIVID 7, GE Vingmed Ultrasound, Horten, Norway), equipped with a 3V-probe for tri-plane acquisition. Patients were scanned in left lateral decubitus position, from the apical window. Care was taken to visualize the true LV apex allowing simultaneous acquisition of the apical 4-, 2- and 3-chamber views. Color-coded TDI was applied to the tri-plane view to assess longitudinal myocardial regional function. Gain settings, filters and pulse repetition frequency were adjusted to optimize color saturation. Sector size and depth were optimized for the highest possible frame rate. At least three consecutive beats were recorded and the images were digitally stored for offline analysis (EchoPac, GE Vingmed Ultrasound, Horten, Norway).

Quantification of LV volumes and ejection fraction

During post-processing, the tri-plane dataset was frozen in end-diastole and the endocardial border was manually traced in the apical 4-, 2- and 3-chamber views respectively. Then, using the same heartbeat, the tri-plane dataset was frozen in end-systole and again the endocardial border was manually traced in the apical 4-, 2- and 3-chamber views. A 3-D LV end-diastolic and end-systolic volume was generated automatically by the software and LV volumes and ejection fraction were reported accordingly (Figure 1).
Quantitative analysis of LV dyssynchrony

During post-processing, the tri-plane color-coded TDI dataset was used to analyze myocardial velocity curves from 12 LV segments derived from information acquired during the same heartbeat. Sample volumes were placed in the basal and mid segments of the septal, lateral, inferior, anterior, posterior and anteroseptal LV walls of the tri-plane dataset to calculate time from the beginning of QRS to peak myocardial systolic velocity ($T_s$). From these 12 measurements a standard deviation was calculated ($T_s$-SD-12) as a measure of intraventricular dyssynchrony. A patient example is provided in Figure 2. Additionally, peak myocardial systolic velocities were measured pre- and post-implantation at the basal septal, lateral, inferior and anterior LV walls.

Implantation of CRT device

The LV pacing lead was inserted transvenously via the subclavian route. First, a coronary sinus venogram was obtained during occlusion of the coronary sinus with a balloon catheter. Next, the LV pacing lead was inserted into the coronary sinus with the help of an 8F 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 a conventional indication for an internal defibrillator existed, a CRT-D device was implanted. At implantation, both the sensing and pacing thresholds (at pulse duration of 0.5 ms) of the LV pacing lead were measured.

Figure 1. Example of 3-D LV volumes, generated from a tri-plane dataset, at baseline (Panel A) and at 6 months follow-up (Panel B) Note the significant decrease of LV volumes and the increase in LV ejection fraction.
Definition of response to CRT

Patients were subsequently divided into clinical responders and non-responders, based on an improvement in NYHA functional class by ≥1 score, 6 months post implantation. Echocardiographic response was defined as a reduction of at least 15% in LV end-systolic volume (reverse LV remodeling) at 6 months follow-up.  

Statistical analysis

All analyses were performed with the statistical software program SPSS 12.0.1 (SPSS Inc, Chicago, IL, USA). 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. Correlations between changes in dyssynchrony or changes in myocardial velocities and LV end-systolic volume and ejection fraction were evaluated with Spearman correlations test. Receiver-operating characteristic (ROC) curves were also analyzed to determine the value of Ts-SD-12 to predict clinical response and reverse LV remodeling after CRT. From these ROC curves, the area under the curve was calculated and presented with 95% confidence intervals (95% CI). A p-value <0.05 was considered significant.

RESULTS

Patient population

A total of 60 consecutive patients (47 men, 13 women) undergoing CRT implantation were included in the study. Mean age was 66 (11) years, 37 patients (62%) had ischemic cardiomyopathy, 23 (38%) had non-ischemic cardiomyopathy. Moreover, 54 patients (90%) were in NYHA class III and 6 (10%) in NYHA class IV. All patients were on optimized medical treatment including beta-blockers (62%), angiotensin converting enzyme inhibitors (85%), diuretics (84%) and aldactone (39%). Mean QRS width was 146 (32) ms. Using tri-plane technology, mean LV end-diastolic volume was 207 (74) ml, mean LV end-systolic volume 160 (71) ml and mean LV ejection fraction 25 (10) %.

Validation of the tri-plane technique

Consistent correlations were found between the Ts data measured using a conventional 2-D method and Ts data measured using triplane technology; r ranging between 0.94 and 0.98 (p <0.001). Bland–Altman analysis shows excellent limits of agreement between LV dysynchrony (Ts-SD-12) measured by 2-D analysis and LV dyssynchrony measured by triplane technology (Figure 3).

Clinical response 6 months post CRT implantation

At 6 months follow-up, 63% of the patients showed clinical improvement as defined by an increase of NYHA class by at least 1 score. The only pre-implantation characteristic differing significantly between responders and non-responders was the extent of LV dyssynchrony as assessed with tri-plane TDI (42 (14) vs 22 (12), p <0.001). Besides an improvement of NYHA class (3.1 (0.3) at baseline, 1.7 (0.5) at follow-up, p <0.0001), clinical responders also showed
improvement in 6-minute walking distance (335 (104) m at baseline, 388 (79) m at follow-up, p = 0.001), quality of life score (32 (19) at baseline, 22 (17) at follow-up, p = 0.001) LV end-diastolic volume (197 (62) ml at baseline, 172 (56) ml at follow-up, p <0.001), LV end-systolic volume (150 (60) ml at baseline, 108 (41) ml at follow-up, p <0.001) and LV ejection fraction (26 (9) % at baseline, 37 (9) % at follow-up, p <0.001). Moreover LV dyssynchrony Ts-SD-12 improved from 42 (14) to 23 (12) (p <0.001).

Reverse LV remodeling at 6 months follow-up

A total of 58% of patients exhibited a reduction of LV end-systolic volume ≥15% within 6 months after CRT implantation (Figure 4). Patients with reverse LV remodeling did not only show improvement of LV end-systolic volume (- 48.6 ml on average) but also a significant decrease of LV end-diastolic diameter (- 31.9 ml on average) and an increase of LV ejection fraction (+ 13.4% on average). Baseline clinical and echocardiographic characteristics of patients without and with reverse LV remodeling are reported in Table 1. The only pre-implantation characteristic differing significantly between patients with and without reverse LV remodeling was the extent of LV dyssynchrony as assessed with tri-plane TDI. Figure 5 shows a relation between the decrease in LV dyssynchrony and the decrease in LV end-systolic volume or the increase in LV ejection fraction.
Tri-plane TDI to predict LV reverse remodeling after CRT

From these ROC curves, the area under the curve was calculated and presented with 95% confidence intervals (95% CIs). A p value, 0.05 was considered significant.

RESULTS

Study group
A total of 60 consecutive patients (47 men, 13 women) undergoing CRT implantation were included in the study. Mean age was 66 (11) years, 37 patients (62%) had ischaemic cardiomyopathy, 23 (38%) had non-ischaemic cardiomyopathy. Moreover, 54 patients (90%) were in NYHA class III and 6 (10%) in NYHA class IV. All patients were receiving optimised medical treatment including β-blockers (62%), angiotensin converting enzyme inhibitors (85%), diuretics (84%) and aldactone (39%). Mean QRS width was 146 (32) ms. Using triplane technology, mean LV end-diastolic volume was 207 (74) ml, mean LV end-systolic volume 160 (71) ml and mean LV ejection fraction 25 (10)%.

Validation of the triplane technique
Consistent correlations were found between the Ts data measured using a conventional 2-D method and Ts data measured using triplane technology; r ranging between 0.94 and 0.98 (p, 0.001). Bland–Altman analysis shows excellent limits of agreement between LV dyssynchrony (Ts-SD-12) measured by 2-D analysis and LV dyssynchrony measured by triplane technology (fig 3).

Pacemaker implantation
CRT device and lead implantation was successful in all patients without major complications (Contak Renewal, Guidant, and Insync Sentry, Medtronic Inc). Two types of LV lead were used: Easytrack (Guidant, St Paul, Minnesota, USA) or Attain (Medtronic Inc, Minneapolis, Minnesota, USA). In 83% of cases a CRT-D device was implanted.

Clinical response 6 months after CRT implantation
At 6 months’ follow-up, 63% of the patients showed clinical improvement as defined by an increase of NYHA class by at least one score. The only pre-implantation characteristic differing significantly between responders and non-responders was the extent of LV dyssynchrony as assessed with triplane TDI (42 (14) vs 22 (12), p, 0.001). Besides an improvement of NYHA class (3.1 (0.3) at baseline, 1.7 (0.5) at follow-up, p = 0.001), clinical responders also showed improvement in 6-minute walking distance (335 (104) m at baseline vs 388 (79) m at follow-up, p = 0.001) and quality of life score (32 (19) at baseline vs 32 (20) at follow-up, p = 0.001).

Table 1. Baseline characteristics of patients without and with reverse LV remodeling at 6 months follow-up.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No reverse LV remodeling</th>
<th>Reverse LV remodeling</th>
<th>p-value</th>
</tr>
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<tr>
<td>Age (years)</td>
<td>65 (10)</td>
<td>67 (12)</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>83% / 17%</td>
<td>77% / 25%</td>
<td>NS</td>
</tr>
<tr>
<td>Ischemic/idiopathic</td>
<td>50% / 50%</td>
<td>31% / 69%</td>
<td>NS</td>
</tr>
<tr>
<td>NYHA III/IV</td>
<td>88% / 12%</td>
<td>94% / 6%</td>
<td>NS</td>
</tr>
<tr>
<td>6-min walking (m)</td>
<td>331 (119)</td>
<td>326 (101)</td>
<td>NS</td>
</tr>
<tr>
<td>Quality of life</td>
<td>37 (19)</td>
<td>32 (20)</td>
<td>NS</td>
</tr>
<tr>
<td>QRS width (ms)</td>
<td>142 (37)</td>
<td>149 (28)</td>
<td>NS</td>
</tr>
<tr>
<td>LVEDV (ml)</td>
<td>210 (91)</td>
<td>206 (65)</td>
<td>NS</td>
</tr>
<tr>
<td>LVESV (ml)</td>
<td>164 (89)</td>
<td>158 (59)</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>25 (11)</td>
<td>25 (9)</td>
<td>NS</td>
</tr>
<tr>
<td>Ts-SD-12</td>
<td>20 (10)</td>
<td>44 (12)</td>
<td>&lt; 0.001</td>
</tr>
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</table>

Results are shown as mean (SD) unless stated otherwise.
LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; NYHA: New York Heart Association; Ts-SD-12: standard deviation of time to peak systolic myocardial velocity measured at 12 left ventricular segments derived from a triplane dataset.

Figure 4. Change in LV volumes and LV ejection fraction at baseline (grey) and at 6 months follow-up (white) in patients exhibiting reverse remodeling (Panels A and C) and those without reverse remodeling (Panels B and D).
Prediction of clinical response after CRT by tri-plane TDI

Overall, Ts-SD-12 measured with tri-plane technology, was significantly larger in clinical responders than in non-responders, indicating severe LV dyssynchrony in the clinical responders. Figure 6A shows the ROC curve illustrating the excellent ability of Ts-SD-12, measured with tri-plane TDI technology, to predict clinical response. An ideal cut-off value for Ts-SD-12 to predict clinical response 6 months after CRT implantation, was defined at 33 ms based on the highest possible sensitivity (89%) and specificity (82%).

Prediction of reverse LV remodeling after CRT by tri-plane TDI

Overall, Ts-SD-12 measured with tri-plane technology, was significantly larger in patients with reverse LV remodeling than in patients without reverse LV remodeling, indicating severe LV dyssynchrony in patients with reverse remodeling. Figure 6B shows the ROC curve illustrating the excellent value of Ts-SD-12, measured with tri-plane TDI technology, to predict reverse LV remodeling. An ideal cut-off value for Ts-SD-12 to predict reverse LV remodeling at 6 months follow-up, was defined at 33 ms based on the highest possible sensitivity (90%) and specificity (83%).

Figure 5. Scatter plots showing the relation between the decrease in left ventricular dyssynchrony (quantified as Ts-SD-12) and (A) decrease in left ventricular end-systolic volume (LVESV); (B) increase in left ventricular ejection fraction (LVEF), 6 months after cardiac resynchronisation therapy. A line is fitted using simple regression analysis and the $r^2$ values are reported, respectively.
DISCUSSION

The findings in the current study can be summarized as follows: 1) the 3-D echo approach permits integrated assessment of LV volumes, LV ejection fraction and LV dyssynchrony; 2) in patients undergoing CRT, LV dyssynchrony was the only predictor of clinical response to CRT; 3) the standard deviation of time to peak myocardial systolic velocity in 12 LV segments (Ts-SD-12) ≥33, calculated from the tri-plane TDI dataset, had a sensitivity of 90% with a specificity of 83% to predict reverse LV remodeling, at 6 months post CRT implantation.

Several authors have emphasized the importance of quantifying the degree of LV dyssynchrony in CRT candidates, to identify potential responders. Earlier studies proposed methods using M-mode or pulsed-wave TDI, but recently, color-coded TDI and techniques derived from color-coded TDI such as TSI and strain rate imaging have gained interest. The majority of color-coded TDI techniques are based on the measurement of time intervals between onset of the QRS complex and peak myocardial systolic velocity. Some authors have compared the activation times of the septal and lateral LV segments; for this approach TDI registration of the apical 4-chamber view, using 2-D technology, is sufficient.

Others used information derived from various LV segments. Yu and co-workers originally described the model (derived from 2D data) using electromechanical activation times of 12 LV segments to quantify LV dyssynchrony. A potential problem with the 2D approach if
one uses the 12-segment model, is the cumbersome data acquisition. At least three separate
color-coded 2D datasets are to be acquired, non-simultaneously. This implies that heart-rate
variability is often neglected, resulting in non-simultaneous comparison of segmental coor-
dination. Moreover, in all CRT studies assessing LV remodeling, LV volumes and LV ejection
fraction were estimated from 2-D datasets with Simpson's biplane method.

Tri-plane imaging is a 3-D technique that integrates data from 3 conventional apical
views. Validation studies have demonstrated that the tri-plane approach is superior to the
bi-plane method and comparable to magnetic resonance imaging for LV volume estimation
\cite{18,19}. Recently a 3D probe became commercially available (GE Vingmed Ultrasound, Horten,
Norway) allowing simultaneous acquisition of a tri-plane dataset and color-coded TDI. In
the present study, we have demonstrated the multi-purpose of this tri-plane TDI dataset in
60 heart failure patients scheduled for CRT implantation. A 3D LV volume was generated
allowing evaluation of volumetric changes 6 months post-implantation, showing reverse LV
remodeling in responders.

Furthermore an established 2-D TDI-based method \cite{7,11} to quantify LV dyssynchrony using
a 12-segment LV model was successfully applied to the tri-plane dataset. Sample volumes
were placed in 12 LV segments and myocardial peak systolic velocities or time to peak systolic
velocities of any LV segment could be compared during the same heartbeat. From these data,
the Ts-SD-12 was calculated. Using 2D technology, Yu et al applied the Ts-SD-12 in 30 CRT
patients and reported that a cut-off value >32.6 ms permitted separation of responders and
non-responders to CRT \cite{7,11}. In a subsequent study the same authors used TSI in a 2-D dataset
to quantify LV dyssynchrony \cite{17}. The Ts-SD-12 was most powerful to predict reverse LV remod-
eling; ROC curve analysis revealed an area of 0.90 with a sensitivity of 87% and a specificity of
81% employing a cut-off value of 34.4 ms. In the present study, the Ts-SD-12 was calculated
from the tri-plane dataset. A ROC curve area of 0.95 was shown with a sensitivity of 90% and
a specificity of 87% for a cut-off value of 33 ms, well in line with the above-mentioned 2-D
studies. The advantage of the tri-plane method is that acquisition of a single tri-plane dataset
allows simultaneous comparison of 12 LV segments during the same heartbeat whereas the
2-D method requires at least 3 acquisitions.

Experience with 3D echocardiographic evaluation of CRT patients is limited. Kapetanakis
et al used real-time 3D echocardiography and calculated a systolic dyssynchrony index
derived from dispersion of time to minimal regional volume in 26 patients undergoing CRT
implantation \cite{20}. The authors noted that patients with a large systolic dyssynchrony index
before implantation experienced the greatest reduction in mechanical dyssynchrony after
CRT, whereas patients without symptomatic improvement had a statistically lower systolic
dyssynchrony index before CRT implantation. The method described by Kapetanakis et al \cite{20}
is based on identification of the last LV region reaching minimum regional volume; the tri-plane
method is based on the assessment of LV dyssynchrony from TDI velocity curves, currently
the most frequently used echocardiographic method to predict benefit from CRT \cite{4}.

Chapter 6
Study limitations

Patients with atrial fibrillation and previous pacemakers were excluded; further studies are needed in these specific patient populations to explore the value of 3-D TDI.

CONCLUSIONS

In the present study, a novel 3-D echocardiographic application, allowing simultaneous acquisition of a tri-plane TDI dataset, was successfully applied in 60 heart failure patients scheduled for CRT. From the tri-plane TDI dataset, quantitative analysis of LV dyssynchrony could be derived as well as LV volumes and ejection fraction. LV dyssynchrony, derived from the tri-plane TDI dataset, was highly predictive for clinical response and LV reverse remodeling after 6 months of CRT.
REFERENCES


13. Refsgaard J. This is a walking test not a talking test: the six minute walking test in congestive heart failure. *Eur Heart J* 2005;26:749-750.


