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CHAPTER 2

PREDICTION OF RESPONSE TO CARDIAC RESYNCHRONIZATION THERAPY COMBINING 2 DIFFERENT 3-DIMENSIONAL ANALYSES OF LEFT VENTRICULAR DYSSYNCHRONY.

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ABSTRACT

Tri-plane tissue synchronization imaging (TSI) and real-time 3-dimensional echocardiography (RT3DE) provide different characterization of LV mechanics and dyssynchrony. Tri-plane TSI assesses differences in time to peak systolic segmental myocardial tissue velocities, whereas RT3DE evaluates differences in time to minimum end-systolic regional volumes. Whether an approach using both 3D modalities predicts better significant reverse remodeling after cardiac resynchronization therapy (CRT) remains unknown. In 166 patients (mean age 66 ± 9 years, 78% male) treated with CRT, baseline LV dyssynchrony was assessed using RT3DE and tri-plane TSI. LV dyssynchrony was defined by systolic dyssynchrony index (SDI) ≥6.4% when assessed with RT3DE and standard deviation of time to peak velocity of 12 segments (Ts-SD-12) ≥33 ms with tri-plane TSI. CRT response was defined by ≥15% reduction in LV end-systolic volume at 6 months follow-up. Mean Ts-SD-12 LV dyssynchrony was 48 ± 26 ms and mean SDI was 8.51 ± 3.81%. Response to CRT was observed in 86.3% of patients showing LV dyssynchrony with both methods. In contrast, 97% of patients who did not show significant LV dyssynchrony with any of the modalities were non-responders (P<0.001). Importantly, SDI and Ts-SD-12 LV dyssynchrony were both independent predictors of response to CRT (P<0.001 for each modality respectively). The assessment of LV dyssynchrony with both modalities showed incremental value for prediction of significant LV reverse remodeling over its assessment with only one modality (chi-square 90.18; P<0.001). In conclusion, the combined use of 2 different 3D modalities to assess LV dyssynchrony permits accurate prediction of response to CRT.

INTRODUCTION

Left ventricular (LV) mechanical dyssynchrony is commonly observed in heart failure patients.[1–3] Evaluation of LV mechanical dyssynchrony has shown to be clinically relevant since it is related to high likelihood of response to cardiac resynchronization therapy (CRT).[4–6] So far, the majority of the trials have used 2-dimensional echocardiographic methods to assess LV dyssynchrony.[5] Recently, the advent of 3-dimensional (3D) imaging techniques has permitted the assessment of dyssynchrony within the entire left ventricle. Tri-plane tissue synchronization imaging (TSI) and real-time 3D echocardiography (RT3DE) have been respectively used to assess LV dyssynchrony and to predict significant LV reverse remodelling after CRT.[7–9] However, these two 3D echocardiographic techniques evaluate different aspects of LV mechanics related to LV dyssynchrony. In particular, the high temporal resolution of tri-plane TSI permits detection of rapid changes in myocardial velocities along the cardiac cycle. In contrast, RT3DE evaluates changes in LV regional volumes along the cardiac cycle. Evaluation of LV dyssynchrony with these two different 3D modalities could potentially provide comprehensive information on LV mechanical activation. Accordingly, the aim of the present study was to evaluate the impact of a comprehensive 3D echocardiographic evaluation of LV mechanical dyssynchrony on prediction of response to CRT.

METHODS

Advanced heart failure patients with left ventricular ejection fraction (LVEF) ≤35% and QRS complex width >120 ms treated with CRT were included in this retrospective analysis.[10] Patients with recent acute coronary syndrome (<3 months) or decompensated heart failure were excluded. The etiology of heart failure was considered ischemic when significant coronary artery disease (>50% stenosis in ≥1 major epicardial coronary artery) was identified on coronary angiography, and/or when a history of prior myocardial infarction or revascularization was noted.

According to the clinical protocol, before CRT implantation, NYHA functional class, quality of life (QoL) using the Minnesota Living with Heart Failure Questionnaire and a 6-minute walk test (6MWT) were evaluated.[11,12] Furthermore clinical evaluation included 3D echocardiography to evaluate LV volumes, LVEF, and LV dyssynchrony in all patients. Particularly, 3D LV dyssynchrony was determined using tri-plane TSI and RT3DE. At 6 months follow-up, LV volumes and LVEF were re-assessed using RT3DE. All clinical data were prospectively entered into the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Centre, Leiden, the Netherlands) and retrospectively analyzed.

Response to CRT was defined as a ≥15% decrease in 3D left ventricle end-systolic volume (LVESV) 6 months after CRT implantation.[13–16] Conversely, patients who did not show such amount of LV reverse remodeling were defined as non-responders. The relative merits of both 3D LV dyssynchrony modalities on the prediction of response to CRT were evaluated at 6 months follow-up.

Patients were imaged using two different ultrasound systems: the iE33 system (Philips Medical Systems, N.A., Bothel, WA, USA) equipped with a X3 matrix phased-array transducer and the Vivid-7 system (GE Healthcare, Horten, Norway) equipped with a 3V phased array transducer. Apical full-volumes datasets were obtained in all patients during breath hold at end-expiration. Scan line density and gain and compression settings were adjusted to optimize image quality. Using the iE33 system and the X3 probe, wide-angle data were acquired and a full large pyramidal volume of the left ventricle (103 x 103º) was obtained from 4-7 R-triggered small real-time subvolumes.[9] Using the Vivid-7 system and the 3V probe, tri-plane images of the left ventricle were acquired. This imaging modality permits simultaneous visualization of the apical 2-, 4- and 3-chamber views of the left ventricle. The inter-plane sector angles were established by default at 60º and were adjusted to obtain adequate orientation of the three apical views. Color-coded TSI was applied to the tri-plane views and sector width and depth were adjusted to optimize frame rate for complete visualization of the entire left ventricle at the highest possible frame rate.[17]

Quantification of 3D LV volumes was performed off-line, using the Q-Lab Advanced Quantification software (Philips Medical System, 2008). The apical full-volume dataset of the left ventricle is automatically cropped displaying the apical 2- and 4-chamber views and the short-axis view. The multi-planar reformation planes are oriented to avoid foreshortening of the LV cavity. Next, the LV apex and the mitral annular plane are identified with 5 reference points at the end-diastolic and end-systolic frames. Subsequently, the software generates a preconfigured ellipse fitted to the endocardial borders for each frame. If needed, endocardial borders were then manually adjusted. Subsequently, a 3D model was automatically generated and 3D LV end-diastolic volume, LVESV and LVEF were calculated.[9]

Tri-plane TSI evaluates LV dyssynchrony based on the analysis of segmental tissue velocities. The analysis of LV dyssynchrony was performed off-line and has been described previously.[8] In order to perform this analysis, the timing of aortic valve opening and closure were first labeled using the pulse-wave velocity of the LV outflow tract. Next, sample volumes were placed the basal and mid segments of the septal, lateral, inferior, anterior, posterior and antero-septal walls of the tri-plane dataset. The time to peak systolic velocity (Ts) for each 12 LV segments was displayed in a bull's eye plot. The LV dyssynchrony index was derived from the standard deviation of time to peak systolic velocity of the 12 segments (Ts-SD-12). A cut-off value of ≥33ms indicates significant LV dyssynchrony (***Figure 1***).[8]

The assessment of LV dyssynchrony was performed off-line using the Q-Lab Advanced Quantification software (Philips Medical System, 2008) 24 hours before CRT implantation. This specific new 3D imaging modality evaluates LV dyssynchrony based on the analysis of regional volumetric changes. Accordingly, the volumetric 3D LV model is automatically sub-divided in 16 pyramidal sub-volumes. The time-volume tracings are displayed for each pyramidal sub-volume and time-to-minimal end-systolic volume is recorded for each segment. The LV dyssynchrony index is derived from the standard deviation of these 16 segmental timings expressed in percentage of the cardiac cycle (Systolic Dyssynchrony Index [SDI]).[18] A SDI cut-off value of ≥6.4% indicates significant LV dyssynchrony (***Figure 1***).[9]

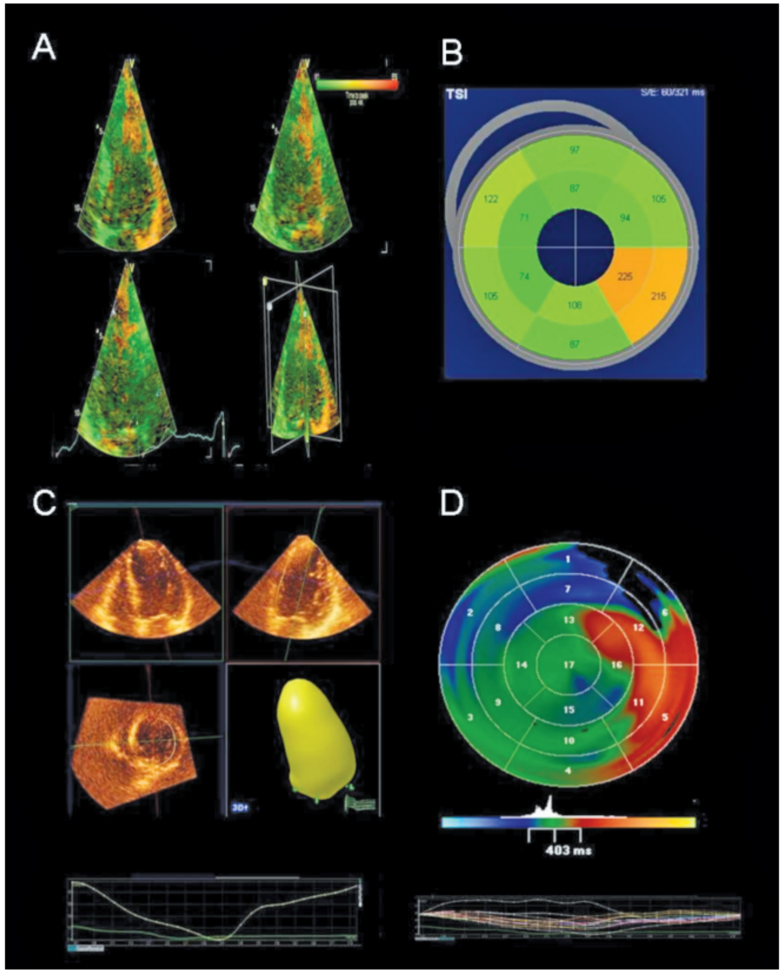
The LV pacing lead was inserted transvenously via the subclavian route. A coronary sinus venogram was obtained using a balloon catheter. Next the LV pacing lead was inserted through the coronary sinus with the help of an 8 Fr-guiding catheter, and positioned as far as possible in the venous system, preferably in a (postero-) lateral vein. The right atrial and ventricular leads were positioned conventionally. CRT-device and lead implantation were successful in all patients without major complications (Contak Renewal, Guidant Corporation; Insync III or Insync Sentry, Medtronic Inc; or Lumax, Biotronik, Berlin). Three types of LV leads were used (Easytrak, Guidant Corporation, St. Paul, Minnesota; Attain, Medtronic Inc., Minneapolis, Minnesota; or Corox, Biotronik, Berlin).

Continuous data are expressed as mean ± SD and were compared with the Student's t test for paired and unpaired data when appropriate. Categorical variables are expressed as number and frequencies and were compared using the chi-squared test. For identification of the independent predictors of response to CRT, a multivariate logistic regression model was created introducing the significant univariate variables as covariates with the stepwise enter method. For each variable, the hazard ratio (HR) and the 95% of confidence intervals (CI) were calculated. The incremental value of both 3D LV dyssynchrony modalities to predict response to CRT over clinical variables was assessed by calculating the global chi-squared test. All statistical analyses were performed with the SPSS software (version 17.0, SPSS Inc, Chicago, IL). For all tests, a P-value <0.05 was considered statistically significant.

Figure 1. **New 3D imaging modalities to assess LV dyssynchrony and LV volumes.**

The upper panels display the assessment of 3D LV dyssynchrony using tri-plane TSI. (A) Identification of each 12 LV segments is performed on the tri-plane dataset using the apical 4, 2 and 3 chambers views. (B) The software provides a color-coded bull's eye showing the timings of peak systolic velocities for each labelled LV segment (in green, the earliest segments, and in orange and red, the most delayed segments). The standard deviation of 12 segments time-to peak systolic velocities (Ts-SD-12) is calculated by the software. In this specific case, the Ts-SD-12 was 51 ms, showing significant 3D LV dyssynchrony.[8]

The lower panels show the acquisition and analysis of 3D LV volumes and dyssynchrony using RT3DE. (C) The endocardial borders are defined and a 3D volumetric model is generated. A time-to-end-systolic volume is shown for the whole LV, and 3D end-diastolic volume, end-systolic volume and ejection fraction are provided by the software. (D) The LV is divided into 16 regional volumes and the time to minimal end-systolic volume curve is displayed for each regional volume. A bull's eye is generated, the earliest segments appearing in blue, the most delayed segments appearing in red. The standard deviation of the 16 segments' time-to-end-systolic volume (systolic dyssynchrony index [SDI]) is calculated automatically. In this case, the SDI was 7.5%, showing significant LV dyssynchrony.[9]



RESULTS

Baseline characteristics of the population are provided in ***Table 1***. According to the cut-off value of tri-plane TSI Ts-SD-12 (≥33ms), 68.1% (n=113) of patients exhibited significant LV dyssynchrony at baseline. Based on the cut-off value for RT3DE SDI (≥6.4%), 69.3% (n=115) of patients exhibited significant pre-implantation LV dyssynchrony (***Figure 2***). Of interest, 57.2% (n=95) of patients exhibited both 3D LV dyssynchrony criteria, 22.9% (n=38) exhibited only one 3D criterion and 19.9% (n=33) did not show any 3D criterion for LV dyssynchrony.

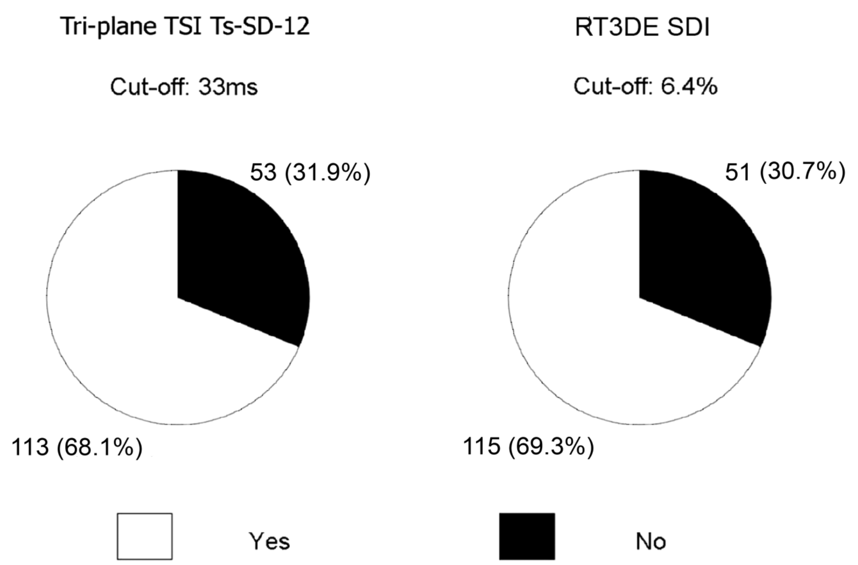
Table 1. Baseline characteristics

Variable	N=166
Age (years)	66±9
Male/Female	130/36
Ischemic/non-ischemic	95 (57%) / 71 (43%)
Sinus rhythm	136 (81.9%)
QRS duration (ms)	152±32
NYHA class	
III	153 (92.2%)
IV	13 (7.8%)
6MWT (m)	346±94
QoL score	28±17
3D Left ventricular end-diastolic volume (mL)	199±62
3D Left ventricular end-systolic volume (mL)	147±50
3D Left ventricular ejection fraction (%)	27±6
Mitral regurgitation grade 3-4	25 (15%)
Tri-plane TSI Ts-SD-12 (ms)	48±26
RT3DE SDI (%)	8.51±3.81
Medication	
Beta-blockers	130 (78.3%)
ACE Inhibitors/ARB	154 (92.8%)
Diuretics/spironolactone	135 (81.3%)

Abbreviations: ACE=Angiotensin II converting enzyme; ARB=Angiotensin receptor blocker; NYHA=New York Heart functional class; QoL=Quality of life questionnaire (Minnesota living with Heart Failure); RT3DE SDI=Real-time 3-dimensional echocardiography systolic dyssynchrony index; TSI Ts-SD-12=Tissue synchronization imaging derived standard deviation of 12 segments time-to-peak systolic velocities; 3D=tri-dimensional; 6MWT=6-minute walk distance test.

Figure 2. **Prevalence of LV dyssynchrony at baseline in the studied population (n=166). Cut-off values for the presence of significant LV dyssynchrony are shown for each of the 3D imaging modalities.**

Abbreviations: RT3DE SDI=Real-time 3-dimensional echocardiography systolic dyssynchrony index; TSI Ts-SD-12=Tissue synchronization imaging derived standard deviation of 12 segments time-to-peak systolic velocities.



At 6 months follow-up after CRT implantation, 62% (n=103) of patients were responders, and 38% (n=63) were non-responders. Comparisons of different baseline variables between responders and non-responders are displayed in ***Table 2***.

Table 2. Baseline characteristics of responders and non-responders to cardiac resynchronization therapy (≥15% decrease in left ventricular end-systolic volume)

Variable	Responders (n=103)	Non-responders (n=63)	P-value
Age (years)	66±9	67±9	0.315
Male/Female	81 (79%) / 22 (21%)	49 (78%) / 14 (22%)	0.929
Ischemic etiology	49 (48%)	46 (73%)	0.001
QRS (ms)	151±30	153±36	0.789
NYHA	3.4±0.2	3.5±0.2	0.185
6MWT (m)	355±91	331±96	0.136
QoL score	28±18	29±18	0.784
3D Left ventricular end-diastolic volume (mL)	203±65	194±57	0.320
3D Left ventricular end-systolic volume (mL)	150±54	142±45	0.355
3D Left ventricular ejection fraction (%)	27±5	27±6	0.997
Mitral regurgitation grade 3-4	13 (13%)	12 (12%)	0.287
Tri-plane TSI Ts-SD-12 (ms)	58±23	32±22	<0.001
RT3DE SDI (%)	9.86±3.87	6.32±2.47	<0.001

Abbreviations: NYHA=New York Heart functional class; QoL=Quality of life questionnaire (Minnesota living with Heart Failure); RT3DE SDI=Real-time 3-dimensional systolic echocardiography dyssynchrony index; TSI Ts-SD-12=Tissue synchronization imaging derived standard deviation of 12 segments time-to-peak systolic velocities; 3D=3-dimensional; 6MWT=distance walked in 6 minutes.

The proportion of responders and non-responders fulfilling the criteria for 3D LV dyssynchrony at baseline was further explored. Of interest, most patients with no criterion for baseline 3D LV dyssynchrony were non-responders (97.0% [n=32]). In contrast, most patients with both 3D LV dyssynchrony criteria were responders (86.3% [n=82]). Finally, patients with only one 3D LV dyssynchrony criterion showed an intermediate probability of response to CRT (52.6% [n=20] responders vs. 47.4% [n=18] non-responders; P<0.001).

Table 3 shows the univariate and multivariate analyses performed to identify the predictors of response to CRT. Importantly, tri-plane TSI Ts-SD-12 and RT3DE SDI were the only independent predictors of response to CRT along with ischemic etiology of heart failure. The relative merits of both 3D LV dyssynchrony modalities to predict response to CRT over clinical variables is presented in ***Figure 3***. The variables introduced in the clinical model were: age, gender, ischemic etiology of heart failure, baseline NYHA functional class and baseline LVEF. Remarkably, the assessment of LV dyssynchrony by either one of the 3D modalities studied had incremental value over clinical evaluation alone to predict response to CRT (change in chi-square from 11.63 to 59.32 [P<0.001]). Additionally, confirmation of LV dyssynchrony by both 3D imaging modalities further increased the accuracy of the model to predict response to CRT (change in chi-square increase to 90.18 with both 3D LV dyssynchrony modalities, P<0.001).

Table 3. Univariate and multivariate predictors of response to cardiac resynchronization therapy (≥15% decrease in left ventricular end-systolic volume)

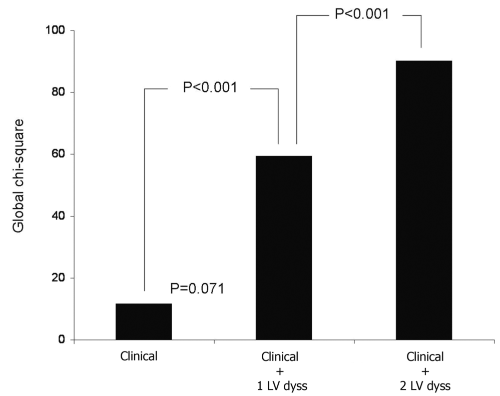
	Univariate		Multivariate	
Variables	OR (95% CI)	P-value	OR (95% CI)	P-value
Age (years)	0.990 (0.957-1.024)	0.558	…	
Gender (male)	0.636 (0.037-11.020)	0.636	…	
Ischemic etiology	0.335 (0.170-0.660)	0.002	0.304(0.122-0.756)	0.010
NYHA	0.835(0.423-1.649)	0.183	…	
Left ventricular ejection fraction (%)	1.000 (0.948-1.054)	0.997	…	
Tri-plane TSI Ts-SD-12	1.028 (1.007-1.049)	<0.001	1.054 (1.032-1.077)	<0.001
RT3D SDI	1.283 (1.110-1.484)	<0.001	1.468 (1.216-1.772)	<0.001

Abbreviations: NYHA = New York Heart functional class; RT3DE SDI = Real-time 3-dimensional echocardiography systolic dyssynchrony index; TSI Ts-SD-12=Tissue synchronization imaging derived standard deviation of 12 segments time-to-peak systolic velocities; 3D=3-dimensional.

Figure 3. Incremental value of assessing LV dyssynchrony with both tri-dimensional modalities to predict response to CRT.

The variables included in the clinical model were: age, gender, etiology of heart failure, baseline NYHA functional class, and LVEF before CRT implantation. The model's global chi-square increases from 11.63 (P=0.071) for the clinical model to 59.32 (P<0.001) with the additional use of either one 3D LV dyssynchrony assessment and to 90.18 (P<0.001) with the extra use of two 3D LV dyssynchrony assessments.

Abbreviations: 3D=3-dimensional; LV dyss=left ventricle dyssynchrony.



DISCUSSION

The present evaluation demonstrated patients who exhibited significant LV dyssynchrony with both tri-plane TSI and RT3DE had a high likelihood of response to CRT (86.3%). Conversely, patients who did not show LV dyssynchrony had a high likelihood of non-response (97%). In addition, each 3D echocardiographic approach to assess LV dyssynchrony were independent predictors of LV reverse remodeling 6 months after CRT, along with ischemic etiology of heart failure. Finally, the presence of significant LV dyssynchrony with both 3D modalities provided the highest accuracy for prediction of response to CRT.

Tri-plane TSI is a new modality derived from TDI that permits LV mechanical dyssynchrony assessment by quantifying the time to peak systolic myocardial velocities of 12 segments simultaneously. The use of tri-plane TSI was described in 49 heart failure patients treated with CRT.[17] The extent of LV dyssynchrony defined by Ts-SD-12 significantly correlated with the amount of LV reverse remodeling within 48 hours after device implantation (r=0.59; P<0.001).[17] Moreover, the robustness of this methodology to assess LV dyssynchrony and predict response to CRT was confirmed in a study including 60 heart failure patients treated with CRT.[8] A cut-off value of 33 ms for tri-plane TSI Ts-SD-12 accurately predicted LV reverse remodeling 6 months after CRT (sensitivity 90%, specificity 83%).[8] The present study extends previous evidence and demonstrates that TSI Ts-SD-12 is an independent predictor of LV reverse remodeling after CRT. Furthermore, the presence of significant tri-plane TSI LV dyssynchrony increased significantly the accuracy of the clinical model for prediction of response to CRT.

RT3DE SDI evaluates LV dyssynchrony by quantifying the time to minimal end-systolic volume for each 16 segments. The merit of RT3DE in assessing LV dyssynchrony and predicting response to CRT has been previously demonstrated.[9,18–21] In a series of 56 patients, the value of SDI to predict acute response to CRT (reduction in LVESV ≥15%) was evaluated.[20] Responder patients showed a larger SDI at baseline compared to non-responder patients (9.7 ± ±4.1% vs 3.4 ± 1.8%; P<0.001).[20] Subsequently, in a study of 51 patients, RT3DE SDI predicted significant LV reverse remodeling at 6 months follow-up with a cut-off value of 6.4% (sensitivity 88%, specificity 85%).[9] Moreover, these results were recently confirmed in a series of 94 heart failure patients treated with CRT.[14] RT3DE SDI accurately identified the patients who showed significant LV reverse remodeling at 12 months follow-up (sensitivity 96% and specificity 88%).[21] The results of the present study support previous data reported in the literature and show that RT3DE SDI was an independent predictor of response to CRT. Moreover, RT3DE SDI increased significantly the accuracy of the clinical model for prediction of response to CRT.

The present study evaluated the combination of two different 3D modalities to assess LV dyssynchrony and subsequently predict the extent of LV reverse remodeling after 6 months of CRT. These two modalities analyze different phenomena of the LV systolic phase. In particular, tri-plane TSI assesses the time differences between peak velocities that occur during the early systolic phase. These early myocardial velocities translate into myocardial motion that eventually leads to effective myocardial contraction. The high temporal resolution provided by tri-plane TSI permits robust assessment of myocardial tissue velocities. In contrast, LV dyssynchrony assessment with RT3DE relies on time differences in regional end-systolic volumes. Specifically, the end-systolic volume is the ultimate consequence of the electromechanical LV activation (peak tissue velocities), occurring at the end of myocardial contraction. Therefore, the occurrence of regional minimal end-systolic volume is relatively delayed compared to the occurrence of myocardial velocities. Thus, tri-plane TSI and RT3DE are two complementary imaging techniques that assess LV dyssynchrony at different time point of the LV systole.

A combined approach including these two complementary modalities to assess LV dyssynchrony to predict response to CRT may be more comprehensive. Remarkably, 97% of patients with no criterion for 3D LV dyssynchrony at baseline were non-responders, whereas 86.3% of patients with both 3D LV dyssynchrony criteria were responders. Moreover, the presence of both 3D LV dyssynchrony criteria predicted response with the highest accuracy when compared to a model with either one 3D modality. The incremental value of assessing LV dyssynchrony with 2 or more imaging modalities to predict response to CRT has been previously proposed.6,22 In a series of 190 heart failure patients treated with CRT, the combination of LV dyssynchrony assessed by color-coded TDI longitudinal strain and by 2D radial strain speckle tracking predicted significant increase in LVEF with higher accuracy (sensitivity 88%, specificity 80%) as compared to one methodology alone (TDI longitudinal strain: sensitivity 72% and specificity 77%; 2D radial strain speckle tracking: 84% sensitivity and 73% specificity; P<0.001).6 More recently, Lafitte et al. developed a strategy combining different indices of LV dyssynchrony for prediction of LV reverse remodeling after CRT.23 Septal-to-posterior wall motion delay by M-mode, radial systole-diastolic overlap, electromechanical delay and electrosystolic delay by TDI, left pre-ejectional delay were the studied LV dyssynchrony parameters. The presence of LV dyssynchrony confirmed by >3 parameters was associated with a specificity >90% and a positive predictive value >65%.23 These results, added to those exposed in the present study, suggest that combination of LV dyssynchrony indices may better identify responders to CRT. However, the present study did not evaluate the impact of LV dyssynchrony assessment with 3D echocardiography on long-term outcome in CRT patients.

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