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ORIGINAL PAPER

Echocardiography for prediction of 6-month and late response to cardiac resynchronization therapy: implementation of stress echocardiography and comparative assessment along with widely used dyssynchrony indices

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Abstract

Non-response cardiac resynchronization therapy (CRT) remains an issue, despite the refinement of selection criteria. The purpose of this study was to investigate the role of stress echocardiography along with dyssynchrony parameters for identification of CRT responders or late responders. 106 symptomatic heart failure patients were examined before, 6 months and 2–4 years after CRT implementation. Inotropic contractile reserve (ICR) and inferolateral (IL) wall viability were studied by stress echocardiography. Dyssynchrony was assessed by: (1) Septal to posterior wall motion delay (SPWMD) by m-mode. (2) Septal to lateral wall delay (SLD) by TDI. (3) Interventricular mechanical delay (IVMD) by pulsed wave Doppler for (4) difference in time to peak circumferential strain (TmaxCS) by speckle tracking. (5) Apical rocking (ApR) and septal flash (SF) by visual assessment. At 6 months there were 54 responders, with 12 additional late responders. TmaxCS had the greatest predictive value with an area under curve (AUC) of 0.835, followed by the presence of both ICR and viability of IL wall (AUC 0.799), m-mode (AUC = 0.775) and presence of either ApR or SF (AUC = 0.772). Predictive ability of ApR and of ICR is augmented if late responders are also included. Performance of dyssynchrony parameters is enhanced, in patients with both ICR and IL wall viability. Stress echocardiography and dyssynchrony parameters are simple and reliable predictors of 6-month and late CRT response. A stepwise approach with an initial assessment of ICR and viability and, if positive, further dyssynchrony analysis, could assist decision making.

Keywords Cardiac resynchronization therapy · Dyssynchrony · Stress echocardiography · Heart failure

Introduction

Cardiac resynchronization therapy (CRT) is a relatively recent advancement in the management of heart failure (HF), that prevents uncoordinated contractions of the left ventricular (LV) walls, through synchronized biventricular (BiV) pacing, from a right ventricular electrode and an additional LV lead, usually targeting the inferolateral (IL) wall [1]. It has been shown to reduce mortality, morbidity and symptoms in a series of randomized trials [2, 3], and it is thus considered an established treatment for symptomatic HF patients (NYHA II–IV) with reduced left ventricular ejection fraction (LVEF < 35%) and prolonged QRS complex (> 130 ms) [4].

Emmanouil Poulidakis and Constantina Aggeli were responsible for the drafting of the manuscript.

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Nonetheless, there is still the issue of non-response to CRT, as a percentage of patients fulfilling selection criteria, in the range of ~30%, do not seem to derive any significant benefit, either in their clinical status or in echocardiographic parameters [5]. Taking into account possible complications of this intervention and the associated cost, alternative selections tools have been sought. To this end, echocardiography has been used extensively to detect the presence of mechanical dyssynchrony, in order to predict response to CRT. The initial enthusiasm from this approach has been set back by the results of multicenter trials like PROSPECT [6], but it is still an area of active research [7], while new echocardiographic applications and novel indices seem promising. At the same time, stress echocardiography, when used to assess inotropic contractile reserve (ICR) and viability of the segment targeted for pacing, seems to add incremental value to dyssynchrony indices, in detecting possible CRT responders [5, 8].

The purpose of this study was to investigate the predictive value for the identification of responders or late responders to CRT of two echocardiographic strategies used separately or in combination. These strategies involved on one hand of the use of low dose dobutamine stress echocardiography (LD-DSE), employed to assess the ICR and the viability of the IL wall, and on the other hand the implementation of widespread and easy to use dyssynchrony parameters.

Methods

Study population

Patients were eligible for this prospective nonrandomized single-center study if they fulfilled the standard indications for CRT, as defined by European guidelines, at the time of the enrollment, which lasted from January 2011 until December 2013 [9, 10], thus consisting of patients with symptomatic HF (NYHA class II–IV) despite maximum tolerated medical therapy, LV systolic dysfunction (LVEF < 35%), and prolonged QRS complex (> 120 ms). As the enrollment period preceded the latest trials and guidelines [11], patients with QRS duration between 120 and 130 ms and those with right bundle branch block were also included. Subjects with both ischemic and non-ischemic cardiomyopathy were studied. Those with recent myocardial infarction or revascularization (< 3 months) or those with reversible causes of HF (e.g. myocarditis) were excluded from the study. During the study period, a total number of 123 patients, who were referred to our department for further evaluation due to new or worsening HF symptoms, were found to be CRT candidates.

Protocol

Study protocol was approved by the Bioethics Committee of the study site. All patients underwent baseline clinical evaluation, including history, comorbidities, physical examination, HF symptom assessment, according to NYHA classification, note of previous hospitalizations, 12-lead surface electrocardiography (ECG), and review of current therapy, to ensure optimal medical therapy for 6 months beforehand. Presence of left bundle branch block (LBBB) on ECG was defined using conventional criteria [12]. Quality of life was assessed with the use of Minnesota Living with heart failure questionnaire (MLHFQ) [13], which has been translated and validated in the subject's language [14], and all patients performed 6-min walk test (6MWT) in a suitable site according to the guidelines of American Thoracic Society [15]. Clinical evaluation was repeated at the 6-month follow-up visit and at the late follow-up visit (between 2 and 4 years). These data were compared with those at baseline. The 6MWT test and MLHFQ questionnaire were repeated only at the 6-month visit. ECGs were also obtained right after implantation and during each subsequent visit.

Echocardiography

CRT candidates underwent echocardiographic examination before implantation, right after the procedure and during follow-up visits, with a commercially available ultrasonography system (Philips iE 33 along with S5-1 transducer) and all measurements were performed according to the guidelines [16]. The study included standard echocardiographic measurements, and calculation of LV end-systolic volume (LVESV), end-diastolic volume (LVEDV), and LVEF was performed using Simpson's biplane method from apical four and two-chamber views, with provisional contrast use to enhance image quality and border delineation.

Mechanical dyssynchrony

Mechanical dyssynchrony was assessed through the use of the following parameters:

Septal to posterior wall motion delay (SPWMD), defined as the difference in time to peak systolic excursion between septal and posterior wall, from parasternal long axis (PLAX) view, with the m-mode cursor set at mid-ventricular level [17]. Color tissue Doppler imaging (TDI) was used to delineate the accurate timing of the events [18].

Interventricular mechanical delay (IVMD) refers to the difference between aortic and pulmonary pre-ejection intervals, each of them defined as the time from QRS onset to the onset of flow in the aorta and the pulmonary artery.

These are measured by pulsed wave Doppler from apical five-chamber view and parasternal short axis (PSAX) at the aortic level respectively [17].

Septal to lateral wall delay (SLD) measured by TDI from apical four-chamber view after positioning of the LV cavity in the center of the sector aligned vertically, in a depth that included the mitral valve annulus. The region of interest is set at the basal segments of opposing LV walls (inferoseptal and anterolateral) and time from QRS onset to the peak of the systolic wave is measured for each of the two. Their difference, the septal-to-lateral delay, expresses dyssynchrony [17, 19].

Difference in time to peak circumferential strain (TmaxCS) cineloops were recorded in PSAX at the level of papillary muscles. These loops were analyzed, on the basis of speckle tracking echocardiography (STE), using commercial software (Q-Station 3.3.2, Philips Healthcare) after selecting two concentric circular regions of interest and semi-automatic tracing of the endocardial and epicardial border respectively. Fine tuning, by visual assessment of the playback of the loop was performed, to ensure consistent tracking throughout the cardiac cycle. The LV wall was divided in six segments and circumferential dyssynchrony was defined as the time difference in between anteroseptal and IL wall [20].

Apical rocking (ApR) and septal flash (SF): their presence was visually assessed by two blinded experienced echocardiographers, and in case of disagreement, the recorded clips were examined by a third echocardiographer [21]. ApR is defined as the movement of the LV apex perpendicular to the longitudinal axis of the LV cavity, usually assessed from apical views [22]. On the other hand, SF describes the characteristic early inward motion of the LV septum, during isovolumic contraction, followed by an outward motion. PLAX on M-mode were used for SF assessment and quantification (large SF: marked and swift inward displacement involving ≥ 50% of septal segments; small SF: early inward septal motion not fulfilling criteria for large SF) [23]. Taking into account that these two phenomena are interconnected [21], we examined not only the presence of each one separately, but also whether either of them was present.

Duration of the echocardiographic examination and calculation of the dyssynchrony indices would take approximately 20–30 depending on the image echocardiographic window. Offline strain analysis of STE data would take another 5–10′.

Stress echocardiography

A standard protocol of LD-DSE with a 17-segment model was adopted. Clinically stable patients underwent echocardiography on ECG and blood pressure monitoring. Dobutamine infusion was started at a dose of 5 mcg/kg/min and doubled every 5 min, up to a maximum dose of 20 mcg/kg/min. The protocol would be terminated upon reaching the maximum dose of dobutamine or 85% of the maximum age-predicted heart rate or upon the apparition of new wall motion abnormalities or side effects (angina, tachycardia, hemodynamic decompensation). ICR was calculated as the percentage improvement in LVEF, relative to baseline figure, with values ≥ 20% considered important [24]. Viability of the IL wall was assessed using the standard practice. Hypokinetic segments and akinetic segments that showed biphasic response or oven improvement by at least one grade during LD-DSE were defined as viable, while thin akinetic and echogenic segments that showed no response to dobutamine were treated as non-viable [25]. Realisation of the LD-DSE protocol would add another 15–20′ to the total examination duration.

Device implantation

Biventricular pacemaker implantation was undertaken using standard techniques, and patients received an LV lead via the transvenous route through coronary sinus delivery systems, to the appropriate lateral vein. The devices employed in this study were either pacemakers or combined devices, at the discretion of the electrophysiologist. Optimization of atrioventricular and interventricular delay, by echocardiographic guidance, was reserved for those who would deteriorate clinically, after the initialization of CRT.

Response to CRT

Response to CRT was defined as greater than 15% decrease in LVESV at the 6-month follow-up visit, which is the usually adopted threshold to indicate reverse remodelling of the LV [6]. Late response was defined as the aforementioned reduction in LVESV, if it was observed only during the late follow-up visit. Clinical response was defined as survival with improvement in symptoms, by at least one category, according to New York Heart Association (NYHA) classification, or an increase by > 25% in 6MWT [26], without any hospitalization due to or associated with worsening heart failure.

Statistical analysis

Statistical analysis was performed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA) software for MS Windows. Quantitative values were expressed as means with standard deviations, or as medians and quartiles, and were compared using paired Student's t-test, if found to be nominal. Otherwise, Wilcoxon Signed Ranks Test or Mann–Whitney rank-sum test were used for paired or individual samples tests respectively. Categorical values were expressed as frequencies

and compared with Fisher's exact test. Predictive ability of continuous variables was checked using logistic regression analysis. Statistical significance was achieved if p values were <0.05, while p values between 0.05 and 0.15 indicated statistical trend. receiver operator curves (ROC) were generated and predictive ability of the examined indices was compared by calculating the area under curve (AUC) and sensitivity and specificity corresponding to the optimal cut off point.

Results

During the study period, 123 patients were screened for CRT implementation. Ten of these did not undergo CRT implantation, as either they withdrew consent or they were deemed candidates for ICD-only therapy. From those who underwent the operation, LV lead insertion was not successful in five (4.4%), while one patient passed away during hospitalization, due to sepsis. In addition, BiV pacing was suspended in one patient, shortly after implantation, due to pro-arrhythmic effect of LV pacing.

Patient population thus consisted of 106 subjects (84 male, 22 female) with an average age of 66.7 (±9.8) years and symptomatic HF (NYHA II-IV) of either ischemic (n = 62) or non-ischemic etiology (n = 14), despite maximum tolerated medical therapy. QRS duration in these patients ranged from 120 to 206 ms and mean LVEF was 30% (±7.8%). Patient baseline characteristics are listed in Table 1.

Not surprisingly, a statistically significant improvement was observed in the overall study cohort, regarding clinical and echocardiographic parameters 6 months after CRT. Likewise, a shortening was observed in the duration of the QRS complex in the study population, between baseline and 6-month assessment (from 160 ms [quartiles 1 to 3: 120–172.5 ms] to 134 ms [120–160 ms], $p = 0.006$) Regression of LVESV (from 120 ml [quartiles 1 to 3:99.5–161.75 ml] to 103.5 ml [quartiles 1 to 3:81.5–145 ml], $p < 0.001$) and LVEF augmentation (from 28 ± 7.9 to 35.1 ± 9.8 $p < 0.001$), were accompanied by an improvement in NYHA classification (from 3 [quartiles 1 to 3: 2–3] to 2 [quartiles 1 to 3: 1–2], $p < 0.001$), quality of life (MLHFQ change from 33 ± 14.3 to 26.1 ± 14.4 $p < 0.001$)

Table 1 Baseline characteristics of study population

	Overall	Responders	Non-responders	p
Demographics and clinical characteristics				
Age (year)	66.7 ± 9.8	67.4 ± 8.3	66 ± 11.2	0.017
Male/female	84/22	44/10	40/12	0.636
Ischemic/non-ischemic	58/48	31/23	27/25	0.697
NYHA (class)	II–IV	0/28/20/6	0/20/30/2	0.002
LVEF (%)	28 ± 7.8	26.7 ± 5.9	29.4 ± 9.4	0.01
LBBB	64 (60.4%)	41 (75.9%)	23 (44.2%)	0.001
Comorbidities				
CKD (GFR < 30 ml/min)	24 (22.6%)	8 (14.8%)	16 (30.8%)	0.098
COPD	10 (9.4%)	8 (14.8%)	2 (3.8%)	0.091
STROKE/TIA	10 (9.4%)	9 (16.6%)	1 (1.9%)	0.015
PAD	6 (5.6%)	2 (3.7%)	4 (7.6%)	0.677
Risk factors				
Hypertension	64 (30.2%)	32 (59.3%)	32 (61.5%)	1
Diabetes	38 (17.9%)	25 (46.3%)	13 (25%)	0.023
Smoking	26 (12.2%)	11 (20.4%)	15 (28.8%)	0.496
Dyslipidemia	62 (29.2%)	31 (57.4%)	31 (59.6%)	0.836
Family history	44 (20.7%)	21 (38.8%)	23 (44.2%)	0.838
Treatment				
B-blockers	99 (93.4%)	50 (92.6%)	49 (94.2%)	1
ACEIs/ARBs	100 (94.3%)	52 (92.9%)	48 (92.3%)	0.433
MRAs	89 (83.9%)	46 (85.2%)	43 (82.7%)	0.795
Diuretic	101 (95.3%)	51 (91.1%)	50 (96.2%)	1

NYHA New York Heart Association, *LVEF* left ventricular ejection fraction, *LBBB* left bundle branch block, *CKD* chronic kidney disease, *GFR* glomerular filtration rate, *COPD* chronic obstructive pulmonary disease, *TIA* transient ischemic attack, *PAD* peripheral artery disease, *ACEIs* angiotensin converting enzyme inhibitors, *ARBs* angiotensin receptor blockers, *MRAs* Mineralocorticoid receptor antagonists

and functional capacity (6MWT change from 318.5 ± 116.5 to 367.7 ± 142.6 p < 0.001).

Using the predefined criteria, 54 (50.9%) patients had evidence of LV reverse remodelling, with a sufficient decrease in LVESV to be classified as "responders". On the other hand, there were 74 subjects (69.8%) showing "clinical response", during the same period. Two of the non-responders died during the 6-month follow-up from progressive heart failure. There were no significant differences in baseline parameters between responders and not responders, except age, LVEF and stroke, which were actually in favor of the non-responder group, NYHA class, which tended to be better among the responders, and frequency LBBB presence, which was examined as an index of response prediction. During long-term follow-up, 12 patients (11.3%) initially classified as non-responders, had evidence of reverse remodelling and thus were classified as "late responders", while 10 patients from the non-responder group passed away.

From the examined predictive criteria, all of them were statistically significant for the prediction of 6-month response, except SLD by TDI, which did not achieve statistical significance in any analysis. Among the criteria, the highest predictive ability, as calculated by the AUC in the ROC analysis, was noted for the TmaxCS (AUC = 0.835) followed by the combined presence of ICR and viability (AUC = 0.799) and SPWMD (AUC = 0.775). ICR alone had a good predictive ability (AUC = 0.768), while that of IL wall viability alone was modest (AUC = 0.587). Nonetheless, the presence of viability was associated with a very high sensitivity for the prediction of response (98.1%). ApR or SF had a decent predictive value (AUC = 0.709 and 0.736 respectively), but the presence of either of them (AUC = 0.772) performed even better. The predictive value of IVMD (AUC = 0.655), although statistically significant, was not better than the one of LBBB presence (AUC = 0.658). IVMD surpassed only the predictive value of QRS duration (AUC = 0.597) (Table 2; Fig. 1).

In the field of late response, however, the aforementioned IVMD and QRS duration failed to achieve statistical significance for the prediction of late echocardiographic response. On the other hand, TmaxCS (AUC = 0.830), ICR (alone or combined with viability, AUC = 0.791 and 0.802

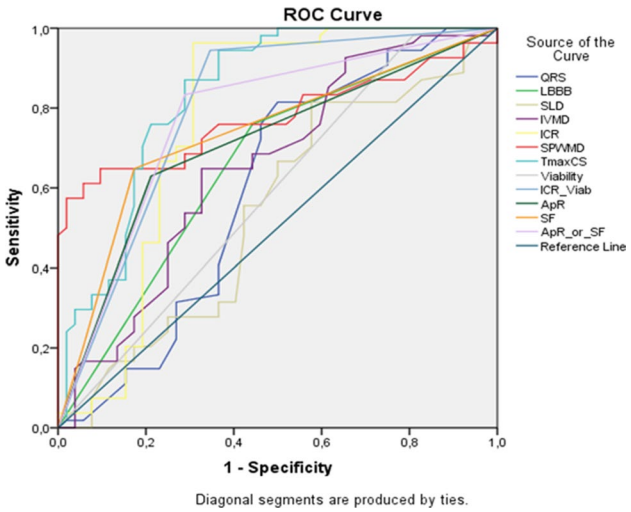

Fig. 1 Roc curve analysis for the prediction of echocardiographic response at 6 months

Table 2 Predictive ability of studied parameters for 6-month response

Parameter	AUC	p-value	Cut off	Sensitivity (%)	Specificity (%)	Published cut off
Echocardiographic response						
QRS	0.597	0.026	145	81.5	50	150
LBBB	0.658	0.001	NA	75.9	55.8	NA
SPWMD	0.775	< 0.001	158	57.4	98.1	130
SLD	0.543	0.485	37.5	81.5	42.3	65
IVMD	0.655	0.032	26.5	64.8	67.3	40
TmaxCS	0.835	< 0.001	53.5	87	71.2	NA
ApR	0.709	< 0.001	NA	36	78.8	NA
SF	0.736	< 0.001	Small SF	64.8	0.827	NA
ApR/SF	0.772	< 0.001	NA	83.3	71.2	NA
ICR	0.768	< 0.001	19.7%	96.3	69.2	20%
Viability	0.587	0.003	NA	98.1	19.2	NA
ICR + viabilty	0.799	< 0.001	NA	94.4	65.4	NA

LBBB left bundle branch block, *SPWMD* septal to posterior wall motion delay, *SLD* septal to lateral delay, *IVMD* interventricular mechanical delay, *TmaxCS* time to maximum circumferential strain, *ApR* apical rocking, *SF* septal flash, *ICR* inotropic contractile reserve

Table 3 Predictive ability of studied parameters for late response and 6-month clinical response

Response	Late response		Clinical response	
Parameter	AUC	p value	AUC	p value
QRS	0.514	0.546	0.433	0.527
LBBB	0.603	0.029	0.619	0.019
SPWMD	0.761	< 0.001	0.645	0.004
SLD	0.482	0.877	0.466	0.660
IVMD	0.634	0.093	0.612	0.295
TmaxCS	0.830	< 0.001	0.754	< 0.001
ApR	0.720	< 0.001	0.715	< 0.001
SF	0.652	0.080	0.614	0.720
ApR/SF	0.754	< 0.001	0.726	< 0.001
ICR	0.791	< 0.001	0.788	< 0.001
Viability	0.617	< 0.001	0.649	< 0.001
ICR + viabilty	0.802	< 0.001	0.810	< 0.001

LBBB left bundle branch block, *SPWMD* septal to posterior wall motion delay, *SLD* septal to lateral delay, *IVMD* interventricular mechanical delay, *TmaxCS* time to maximum circumferential strain, *ApR* apical rocking, *SF* septal flash, *ICR* inotropic contractile reserve

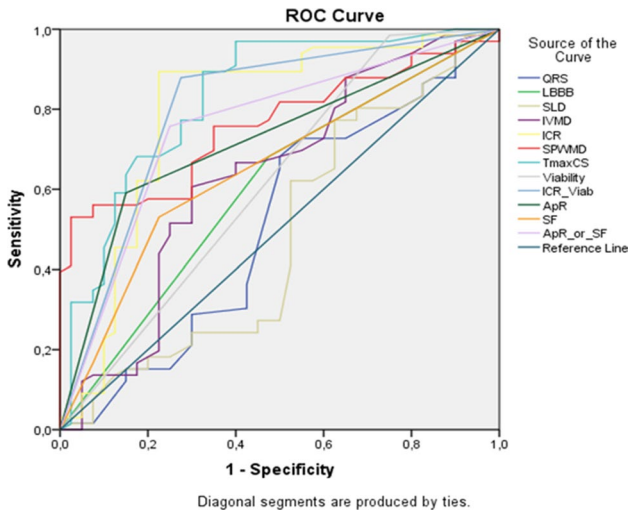

Fig. 2 Roc curve analysis for the prediction of late echocardiographic response

respectively), SPWMD (AUC = 0.761) and ApR (alone or combined with SF, AUC = 0.720 and 0.754 respectively) retained a high diagnostic accuracy even in the setting of late response, while SF alone did not achieve statistical significance. Finally, clinical response was more variable, with many indices having an inferior performance in its prediction, except ApR, LBBB, ICR and viability (alone or combined) (Table 3; Fig. 2).

Interestingly enough, in the subpopulation without LBBB in the surface ECG, the studied parameters gave promising results, as both dyssynchrony indices (TmaxCS, SPWMD, ApR ± SF) and LD-DSE parameters predicted outcomes with reasonable accuracy (Table 4).

Taken into account that the absence of either ICR or viability of the IL wall was associated with a negative predictive value of 91.9%, we performed a further analysis of CRT response prediction by dyssynchrony parameters in the subgroup of patients that had both ICR and IL wall viability. That resulted, in most cases, in a further boost in their predictive ability, in all the three settings regarding patient response (Table 5).

Discussion

As expected, study population derived a substantial benefit from pacing, in terms of symptoms, functional capacity and quality of life, which was accompanied by an improvement in echocardiographic parameters and a decrease in QRS duration, compatible with the benefit described in large randomized clinical trials [2]. The present study indicates that this benefit can be reliably predicted through the use of LD-SE and easily implemented dyssynchrony indices, both in short and, more importantly, on long-term basis.

To our knowledge, this is one of the few studies that compare the predictive value of LD-DSE in identifying CRT responders with that of multiple commonly used echo modalities and indices. While there have been numerous reports about the value of ICR and about the importance of viability in the myocardial wall targeted for BiV pacing [27, 28], only in a few reports has the predictive ability of ICR been comparatively evaluated with the dyssynchrony parameters [24, 29]. In both cases, ICR and intraventricular dyssynchrony, as well as SF in the recent one, were predictive of response, which was not true for parameters based on TDI or pulsed-wave Doppler. In the latter study, combination of ICR and dyssynchrony could further improve sensitivity and specificity. Results presented in our study are, in general, consistent with the literature, and confirmed by the results of a meta-analysis encompassing studies investigating ICR relation to CRT response [8].

The most important aspect, however, of our study, is that it addresses the issue of late response to CRT. It has already been noted in literature that volumetric measurements at 6 months might be premature to rule out CRT response [30]. There is also a growing number of publications noting the existence of a patient subgroup, usually referred to as "late responders", who present with signs of clinical and echocardiographic improvement only after long follow-up [31, 32]. Our current study went a step further, as we assessed the value of baseline echo parameters in predicting not only mid-term but also late response to CRT.

Regarding the choice of dyssynchrony parameters, we deliberately selected indices that are widely used and easily

Table 4 Predictive ability of dyssynchrony indices in the sub-population with non-LBBB

Response	Response		Late response		Clinical response	
Parameter	AUC	p value	AUC	p value	AUC	p value
LBBB	0.495	0.885	0.300	0.029	0.338	0.061
SPWMD	0.760	0.001	0.736	0.003	0.579	0.116
SLD	0.458	0.506	0.328	0.098	0.532	0.860
IVMD	0.564	0.955	0.400	0.111	0.509	0.399
TmaxCS	0.898	< 0.001	0.917	< 0.001	0.833	< 0.001
ApR	0.619	0.041	0.595	0.078	0.625	0.022
SF	0.696	0.116	0.595	0.003	0.569	0.257
ApR/SF	0.739	0.002	0.643	0.040	0.653	0.030
ICR	0.745	< 0.001	0.591	0.028	0.690	0.003
Viability	0.638	0.035	0.690	0.002	0.722	< 0.001
ICR + viabilty	0.828	< 0.001	0.714	0.005	0.785	< 0.001

LBBB left bundle branch block, *SPWMD* septal to posterior wall motion delay, *SLD* septal to lateral delay, *IVMD* interventricular mechanical delay, *TmaxCS* time to maximum circumferential strain, *ApR* apical rocking, *SF* septal flash, *ICR* inotropic contractile reserve

Table 5 Predictive ability of dyssynchrony indices in the sub-population with positive ICR and viability of the inferolateral wall

Response:	Response		Late response		Clinical response	
Parameter	AUC	p value	AUC	p value	AUC	p value
QRS	0.669	0.024	0.737	0.007	0.529	0.440
LBBB	0.650	0.022	0.680	0.027	0.632	0.161
SPWMD	0.786	< 0.001	0.838	0.001	0.734	0.051
SLD	0.464	0.571	0.418	0.457	0.358	0.395
IVMD	0.678	0.021	0.759	0.005	0.820	0.008
TmaxCS	0.841	< 0.001	0.916	< 0.001	0.816	0.003
ApR	0.667	0.015	0.791	< 0.001	0.743	0.019
SF	0.833	< 0.001	0.793	0.001	0.707	0.054
ApR/SF	0.765	< 0.001	0.877	< 0.001	0.824	0.001

LBBB left bundle branch block, *SPWMD* septal to posterior wall motion delay, *SLD* septal to lateral delay, *IVMD* interventricular mechanical delay, *TmaxCS* time to maximum circumferential strain, *ApR* apical rocking, *SF* septal flash

implemented. While indices based on complex analysis of echocardiographic data, such as the cross-correlation analysis, the temporal uniformity of strain and the systolic stretch index, have been successfully tested, mostly in single centre studies [33–35], the rate of adoption in every day clinical practice, especially outside the context of a specialised tertiary echo laboratory, has not been high.

SPWMD has been repeatedly tested in various trials usually with a modest predictive value [6, 18]. In our study, it turned out to have a higher diagnostic accuracy, resembling the results of the initial investigators [36]. IVMD is also a simple index, proven to be an independent predictive factor, in the aforementioned trials, when tested in parallel to ICR. From the plethora of TDI-based methods, we selected the SLD, which is the simplest one, and perhaps that could explain the poor performance of this approach. Perhaps, an index examining more globally the LV, like the "dyssynchrony index" described by Yu et al., could have resulted in better performance [37].

In the field of STE, the choice of circumferential strain, over radial strain, has mostly due to the low reproducibility of radial strain. Despite, the fact that numerous reports, including the multicentre STAR study, point out the benefit of using radial strain over circumferential or longitudinal [20], several other studies have shown that radial strain is the least reproducible [38]. Moreover, radial strain was not available in the software package we used for strain analysis (Philips Q-Station 3.3.2). On the other hand, circumferential strain has been successfully used, with incremental value, by the investigators of the START trial, as they demonstrated that the inclusion of the standard deviation of time from QRS onset to first peak on the circumferential strain curves could further improve the predictive capacity of a multivariable logistic regression model, consisting of clinical

and echocardiographic variables [39]. The same group of investigators had previously shown that this dyssynchrony parameter, measured in PSAX at mid-ventricular level, had superior performance (AUC = 0.76) than other STE indices based on radial or longitudinal strain [40]. In any case, the results of our study could be added to the growing body of evidence favoring the adoption of STE methodology for dyssynchrony detection. Other forms of strain, based on apical views, have also been successfully used in significant trials. In the MUSIC study, Lim et al. propose the use of "Strain delay index", which they define as the sum of difference between end-systolic and peak strain across the 16 segments [41]. While this index seems promising and advantageous over the assessment of dyssynchrony by 12-segment standard deviation of peak longitudinal strain, it was our choice to select indices that would be easier to measure and thus to implement in everyday clinical practice. Finally, it is worth noting that measurement of transverse strain, calculating the relative myocardial thickening from apical views, can be an alternative approach, as shown in a subset of the MADIT-CRT trial, as improvement in this dyssynchrony parameter seems to correlate with improvement in clinical outcomes [42].

Finally, our results are in line with previous reports on the predictive potential of visually assessed parameters, such as ApR and SF. Studies based on non-contact mapping have revealed a characteristic U-shaped activation pattern in patients with conduction abnormalities, such as LBBB, which is highly correlated with the presence of SF [23]. This inhomogeneity in the sequence of regional myocardial shortening also produces typical apical contraction patterns, identified as ApR [43]. These two phenomena frequently coexist, and Stankovic et al. report that 83% of the patients who were positive for the one criterion were also positive for the other, while 8.4% and 8.6% had isolated SF or ApR respectively [21]. That was the conceptual basis for us to examine these indices in combination, which appeared to have a superior diagnostic accuracy than either of them alone. Finally, the superiority of these indices over the mere presence of LBBB on ECG could be explained by the work of Lumens et al., as SF and ApR could discriminate between LBBB caused by electromechanical substrate, and thus amendable by CRT, and that related to non-electrical hypocontractility or scar substrate, unlikely to respond to BIV pacing [35].

Limitations

The study was observational and non-randomized, with a rather small patient sample. So, caution is warranted before any attempt to generalize the results is made. In our study, there was a rather small percentage of responders (50.9%), while clinical response was more in line with large clinical trials. This could be attributed to the fact that patients with QRS duration between 120 and 130 ms were enrolled, while the incidence of LBBB in our study population was only 60.4%, reflecting the selection criteria before the latest guidelines. Also, despite the fact that long follow-up was one the main characteristic of this study, primary analysis of predictive value was based on the 6-month response results. As mentioned earlier, radial strain analysis was not feasible with the software package used, although it was our decision to prefer circumferential strain analysis, due to issues of non-reproducibility of radial strain. Viability on the other hand, was assessed solely on echocardiographic examination, and not by magnetic resonance imaging with late gadolinium enhancement. Finally, the cut off values calculated in our study, for some of the dyssynchrony indices used, differ considerably from those already published, and that could possibly be attributed to the sample size.

Conclusion

LD-DSE and dyssynchrony parameters outperformed ECG criteria for CRT patient selection. LD-DSE results along with indices like TmaxCS, SPWMD, ApR and SF, are simple and reliable predictors of CRT response, not only within 6 months, but of late response as well. A stepwise approach with an initial assessment of ICR and viability in CRT candidates and further dyssynchrony analysis, in those with both ICR > 20% and viable IL wall, could help decision making for possible CRT in equivocal cases.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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