ORIGINAL RESEARCH ARTICLE

Acute correction of electromechanical dyssynchrony and response to cardiac resynchronization therapy

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Abstract

Aims   Echocardiographic measures of dyssynchrony at baseline have not demonstrated a good ability to predict response to cardiac resynchronization therapy (CRT). The purpose of this study was to determine if the acute correction of electromechanical dyssynchrony, assessed by the change in simple pulsed-Doppler measures, was related to CRT response at 6 months.
Methods and results   Echocardiography was performed at baseline and at pre-discharge after CRT implantation. Intraventricular, interventricular, and atrioventricular dyssynchrony were evaluated by the left pre-ejection interval (LPEI), the interventricular mechanical delay, and the ratio of left ventricular filling time to RR interval, respectivelxy. A patient was considered responder if he/she was alive without hospitalization for heart failure and had an absolute increase of left ventricular ejection fraction (LVEF) >5 points. Forty-eight patients (mean age 67 ± 11 years, 73% male, mean LVEF 30 ± 5%) were included. CRT led to an acute correction of intraventricular and interventricular dyssynchrony but not to an acute correction of atrioventricular dyssynchrony. There were 31 (65%) responders at 6 months. Two factors were independently associated with CRT response in multivariate analysis: ischemic cardiomyopathy (odds ratio 0.19, 95% confidence interval 0.04–0.87; *P*= 0.032) and delta LPEI (odds ratio 1.03 per 1 ms decrease, 95% confidence interval 1.01–1.05; *P* = 0.007). By receiver operating characteristic analysis, the optimal cut-off value of delta LPEI was −16 ms. The proportion of responders in patients without ischemic cardiomyopathy and with a delta LPEI greater than −16 ms was 85%.
Conclusions   Acute correction of intraventricular electromechanical dyssynchrony evaluated by the LPEI predicted CRT response at 6 months.

Introduction

Cardiac resynchronization therapy (CRT) is an established treatment for patients with symptomatic heart failure and left ventricular (LV) dysfunction.[1,2] Patient selection currently relies on electrocardiographic markers, QRS duration, and morphology. The multicentre Predictors of Response to CRT study[3] demonstrated that echocardiographic parameters of mechanical dyssynchrony had, in general, unsatisfactory reproducibility and usefulness to identify clinical and echocardiographic responders to CRT. As a consequence, mechanical dyssynchrony for patient selection has not been incorporated into guidelines or standard of care.[4,5] However, the three, simple, pulsed-Doppler parameters tested in the Predictors of Response to CRT study were interpretable in most examinations, showed good reproducibility, and had a statistically significant—although modest—performance in predicting outcomes. These parameters were left pre-ejection interval (LPEI), interventricular mechanical delay (IVMD), and LV filling time (LVFT)/RR interval. They are termed electromechanical because they incorporate electrocardiographic and contraction timings and evaluate intraventricular, interventricular, and atrioventricular dyssynchrony, respectively.

Response to CRT is multifactorial and may depend on the effectiveness of the delivered biventricular pacing, that is, its impact on baseline dyssynchrony. This has been suggested for electrical resynchronization as manifested by the relation between the magnitude of QRS narrowing and response to therapy.[6] Whether effective electromechanical resynchronization might influence outcomes has been less investigated.

The objective of this study was to determine if the acute correction of electromechanical dyssynchrony assessed by the change in the aforementioned simple echocardiographic measures was related to CRT response at 6 months.

Methods

Patient selection

Patients were included in this prospective, observational, single-centre study if they had a standard indication for CRT.:[4] LV ejection fraction (LVEF) ≤35%, New York Hear Association Class 2, 3, or ambulatory class 4, QRS width ≥ 120 ms, despite optimal medical therapy. Both *de novo* implantations and upgrades were included. Patients in permanent atrial fibrillation underwent concomitant atrioventricular junction ablation to ensure complete CRT delivery and could be included. Exclusion criteria were patients listed for cardiac transplantation, expected survival less than 6 months, and pacing for advanced atrioventricular block.

Cardiac resynchronization therapy response

The primary endpoint was CRT response at 6 months. A patient was considered responder if he/she was alive, had not been hospitalized for heart failure, and had an absolute increase of LVEF >5 points. For the purpose of this study, patients who experienced lead dislodgement or extraction during follow-up, that is, modification or withdrawal of the initial resynchronization, were excluded from analysis.

Echocardiographic measurements

Transthoracic echocardiography was performed at baseline, at Day 1 or 2 post-implantation (pre-discharge), and at 6 months using Vivid 6 or 9 machines (General Electric Healthcare, Massachusetts, USA) by a physician blinded to the patient's clinical evolution. In addition to the standard examination, simple electromechanical dyssynchrony parameters were recorded on baseline and pre-discharge examinations.[3,7] Intraventricular dyssynchrony was evaluated by the LPEI and was considered present if LPEI ≥140 ms. Interventricular dyssynchrony was evaluated by the IVMD, calculated as the difference between LPEI and right pre-ejection interval, and was considered present if IVMD ≥40 ms. Atrioventricular dyssynchrony was evaluated in patients in sinus rhythm by the LVFT/RR ratio and was considered present if ≤40%.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as counts with percentages. Comparison between groups were performed with the Mann–Whitney test for continuous variables and a Chi-Square test or Fischer exact test for categorical variables, as appropriate. Comparison of dyssynchrony parameters at baseline and pre-discharge examinations was performed with a Wilcoxon signed-rank test for continuous variables and a McNemar test for categorical variables.

Multivariate analysis using backward logistic regression was performed to identify factors independently associated with CRT response. Factors with $P < 0.10$ in univariate analysis were entered in the model.

A receiver operating characteristic curve was generated to evaluate the diagnostic accuracy of the parameter identified in multivariable analysis in identifying CRT response and to determine the optimal cut-off value. This cut-off value was used to dichotomize the population to groups ≤ cut-off and > cut-off. A P value <0.05 using two-tailed analysis was considered statistically significant. Statistical analyses were performed with MedCalc v19.0.5 (MedCalc Software bvba, Ostende, Belgium).

This study complies with the Declaration of Helsinki. All patients provided written informed consent, and this study was approved by the local ethics committee.

Results

Patient population

Forty-eight patients (mean age 67 ± 11 years, 73% male) were included (*Table 1*). Ischemic cardiomyopathy was present in 20 (42%) patients. Mean LVEF was 30 ± 5%, and 32 (67%) patients had left bundle branch block.

There were 31 (65%) *de novo* implantations and 17 (35%) upgrades. LV lead vein location was lateral in 39 (81%) patients. Fourteen patients (29%) were in permanent atrial fibrillation at the time of implantation, and all underwent immediate atrioventricular junction ablation.

Acute correction of electromechanical dyssynchrony

At baseline, intraventricular and interventricular dyssynchrony were present in 44 (92%) and 25 (53%)

Table 1 Patient characteristics

	Total population $N = 48$	Non-responders $N = 17$	Responders $N = 31$	P
Age	68 ± 11	68 ± 10	67 ± 12	0.81
Male	35 (73%)	14 (82%)	21 (68%)	0.33
Obesity	15 (32%)	5 (31%)	10 (32%)	1
NYHA classification				
2	16 (33%)	5 (29%)	11 (35%)	0.92
3	32 (67%)	12 (71%)	20 (65%)	
Ischemic cardiomyopathy	20 (42%)	11 (65%)	9 (29%)	0.03
Atrial fibrillation	14 (29%)	5 (29%)	9 (29%)	1
QRS duration (ms)	165 ± 29	165 ± 27	165 ± 31	0.89
LBBB	32 (67%)	8 (47%)	24 (77%)	0.07
Upgrade	17 (35%)	6 (35%)	11 (35%)	1
LV lead in lateral vein	39 (81%)	16 (94%)	23 (92%)	1
LVEDV (ml)	205 ± 60	210 ± 64	202 ± 59	0.76
LVESV (ml)	142 ± 47	144 ± 46	140 ± 49	0.79
LVEF	30 ± 5	30 ± 5	29 ± 5	0.42
TAPSE <17	17 (35%)	9 (53%)	8 (28%)	0.16
MR ≥ 2	17 (35%)	7 (41%)	10 (32%)	0.76
Creatinin	123 ± 67	127 ± 71	121 ± 66	0.78
Sodium	137 ± 7	135 ± 10	137 ± 4	0.87
Haematocrit	42 ± 4	42 ± 5	41 ± 4	0.47
NT-proBNP	3399 ± 3699	4106 ± 4733	3045 ± 3099	0.50
ACEI/ARB	41 (85%)	15 (88%)	26 (84%)	1
Betablocker	44 (92%)	16 (94%)	28 (90%)	1
Aldosterone antagonists	29 (60%)	9 (53%)	20 (65%)	0.63
Diuretics	43 (90%)	16 (94%)	27 (87%)	0.64
Ivabradine	6 (12%)	1 (6%)	5 (16%)	0.4
Amiodarone	12 (26%)	4 (24%)	8 (27%)	1
Anticoagulant	23 (49%)	7 (41%)	16 (53%)	0.62
Antiplatelet	20 (42%)	10 (59%)	10 (33%)	0.16

ACEI/ARB, ACE-inhibitors/angiotensin receptor blockers; LBBB, left bundle branch block; LV, left ventricle; LVEDV, LV end-diastolic volume; LVESV, LV end-systolic volume; LVEF, LV ejection fraction; MR, mitral regurgitation; NT-proBNP, N-terminal pro BNP; NYHA, New York Heart Association; TAPSE, tricuspid annular plane systolic excursion.

patients, respectively (*Table 2*). Among the 32 patients in sinus rhythm in whom LVFT was measured, atrioventricular dyssynchrony was present in five (16%) patients. Acute correction of intraventricular and interventricular dyssynchrony was observed, both in absolute values and in the proportion of patients meeting the criterion (*Table 2*). There was no acute correction of atrioventricular dyssynchrony.

Cardiac resynchronization therapy response

There were 31 (65%) responders. Two patients died (one of heart failure and one of digestive cancer), and two patients

were hospitalized for heart failure. Responders had less often ischemic cardiomyopathy than non-responders (*Table 1*). Other clinical parameters and baseline LV volumes and LVEF were not different between groups. Responders had greater intraventricular and interventricular dyssynchrony at baseline (*Table 3*). Compared to non-responders, responders had a greater acute correction of intraventricular dyssynchrony (delta LPEI +12 ± 49 ms vs. −33 ± 38 ms, P = 0.004) and of interventricular dyssynchrony (delta IVMD +9 ± 47 ms vs. −27 ± 36 ms, P = 0.01) (*Table 3*). There was no difference in acute correction of atrioventricular dyssynchrony between responders and non-responders. Electromechanical dyssynchrony at pre-discharge, that is, residual dyssynchrony after CRT, was not different between responders and non-responders.

Table 2 Acute correction of electromechanical dyssynchrony

	Baseline	Pre-discharge	P
LPEI (ms)	170 ± 33	153 ± 35	0.004
LPEI ≥140 ms	44 (92%)	29 (60%)	<0.001
IVMD (ms)	38 ± 40	23 ± 21	0.02
IVMD ≥40 ms	25 (53%)	10 (21%)	0.003
LVFT (%) *n* = 32	47 ± 7	49 ± 11	0.65
LVFT≤40%	5 (16%)	6 (17%)	0.69

IVMD, interventricular mechanical delay; LPEI, left pre-ejection interval; LVFT, left ventricular filling time.

Multivariate analysis

Two factors remained significantly associated with CRT response in multivariable analysis: ischemic cardiomyopathy (odds ratio 0.19, 95% confidence interval 0.04–0.87; P = 0.032) and delta LPEI (odds ratio 1.03 per 1 ms decrease, 95% confidence interval 1.01–1.05; P = 0.007).

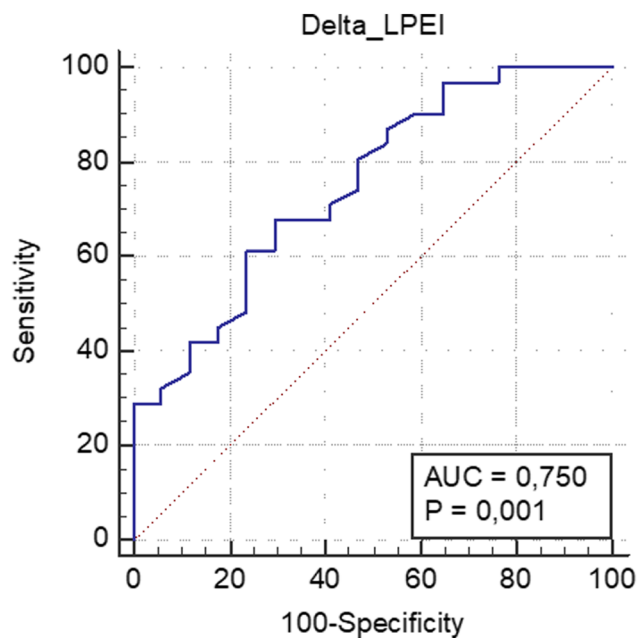**Table 3** Comparison of electromechanical dyssynchrony parameters between responders and non-responders.

	Non-responders N = 17	Responders N = 31	P
Baseline parameters			
LPEI (ms)	153 ± 21	180 ± 35	0.009
LPEI ≥140 ms	15 (88%)	29 (94%)	0.61
IVMD (ms)	17 ± 39	49 ± 37	0.01
IVMD ≥40 ms	4 (25%)	21 (68%)	0.013
LVFT/RR (%) n = 32	49 ± 7	45 ± 7	0.14
LVFT/RR ≤ 40%	1 (8%)	4 (20%)	0.63
Pre-discharge			
LPEI (ms)	165 ± 45	147 ± 28	0.31
LPEI ≥140 ms	11 (65%)	18 (58%)	0.89
IVMD (ms)	25 ± 21	21 ± 22	0.52
IVMD≥40 ms	5 (29%)	5 (16%)	0.29
LVFT/RR (%)	49 ± 12	49 ± 11	0.77
LVFT/RR ≤ 40%	2 (15%)	4 (18%)	1
Difference baseline-Pre-discharge			
Delta LPEI (ms)	12 ± 49	−33 ± 38	0.004
Delta LPEI >10 ms	7 (41%)	21 (68%)	0.14
Delta IVMD (ms)	9 ± 47	-27 ± 36	0.01
Delta LVFT/RR n = 28	−1 ± 16	1 ± 9	1

IVMD, interventricular mechanical delay; LPEI, left pre-ejection interval; LVFT, left ventricular filling time.

Proportion of responders according to the presence of ischemic cardiomyopathy and to the change of delta left pre-ejection interval

Receiver operating characteristic analysis (*Figure 1*) showed that delta LPEI was able to identify CRT response (area under the curve: 0.750, 95% confidence interval 0.605–0.864; P =

Figure 1 Receiver operating characteristic (ROC) analysis for the ability of delta left pre-ejection interval (LPEI) to predict cardiac resynchronization therapy (CRT) response.
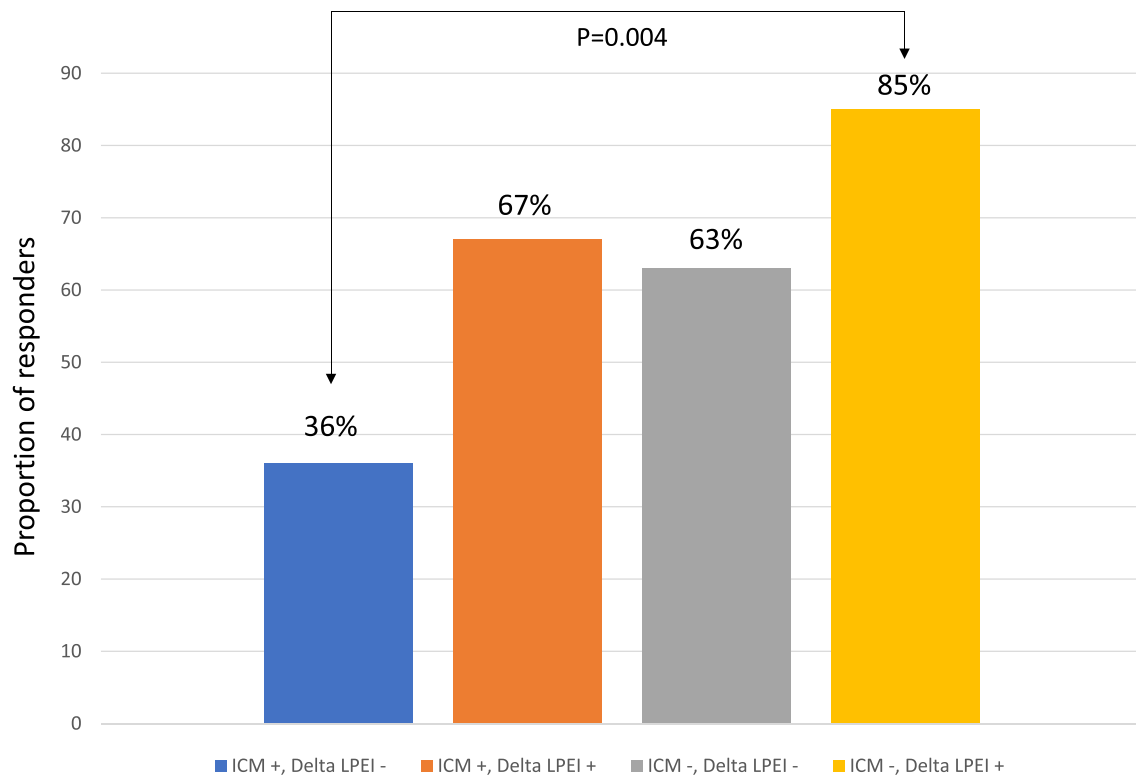

0.001). The optimal cut-off value was less than or equal to −16 (i.e. a decrease of LPEI of 16 ms between baseline and pre-discharge), with a sensitivity of 68% and specificity of 71%. Patients were categorized according to this cut-off value and to the presence of ischemic cardiomyopathy (*Figure 2*). Patients with non-ischemic cardiomyopathy and with a delta LPEI greater than −16 ms had a higher response rate than patients with an ischemic cardiomyopathy and a delta LPEI less than −16 ms (85 vs. 36%, P = 0.004).

Discussion

The main result of this study was that acute correction of electromechanical intraventricular dyssynchrony evaluated by a simple echocardiographic parameter predicted CRT response at 6 months.

In this study, baseline LPEI and IVMD were predictors of CRT response in univariate analysis but not in multivariate analysis. There has been a debate about the value of echocardiographic parameters of mechanical dyssynchrony in predicting CRT response. The randomized Cardiac Resynchronization–Heart Failure trial required in patients with a QRS duration between 120 and 149 ms the presence of two of the three following criteria: LPEI >140 ms, IVMD >40 ms, and a diastolic overlap of LV lateral wall contraction.[1] In subgroup analysis, patients with QRS duration <160 ms did not derive benefit in terms of survival without hospitalization for a major cardiovascular event.[1] Likewise, Bordachar *et al.*[8] showed that these three parameters measured at baseline did not predict clinical and

Figure 2 Responder rates according to the etiology of heart failure and to the magnitude of LPEI reduction. Patients without ischemic cardiomyopathy and with a delta LPEI greater than ≤-16ms had a higher response rate than patients with an ischemic cardiomyopathy and a delta LPEI less than -16ms (85% vs. 36%, P=0.004).

echocardiographic response to CRT, both when considered alone or in combination. While other studies using the same echocardiographic parameters showed conflicting results,[9] our results are in line with the greatest body of evidence suggesting that no parameter can currently be recommended for patient selection.

Our study suggests that the modification of baseline dyssynchrony by biventricular pacing could be a better predictor of CRT response than baseline dyssynchrony. Response to CRT depends on the myocardial substrate[10] and on the interplay between lead positions and the underlying substrate.[11,12] A recent study showed that improvement in LV end-systolic volume and global longitudinal strain at 6 months post-CRT was associated with better survival at 8 years.[13] It would be interesting to be able to predict CRT response at an even earlier time point after device implantation, immediately after implantation. Few studies have examined the impact of acute resynchronization on outcomes.[14–16] Bleeker *et al.*[14] assessed LV dyssynchrony with tissue-Doppler imaging and considered it present if the maximum delay between peak systolic velocities among the four walls within the LV was of 65 ms or greater. Only responders (defined as a >10% reduction of LV end-systolic volume at 6 months) demonstrated a significant reduction of

dyssynchrony immediately after implantation. Stankovic *et al.*[15] showed that correction of septal flash and apical rocking by CRT were associated with reverse remodelling at 1 year. Wang *et al.*[16] showed that echocardiographic responders at 6 months had a significant reduction in acute discoordination assessed with speckle-tracking echocardiography.

In our study, acute correction of LPEI was associated with a positive response to CRT. Compared with the parameters used in the aforementioned studies, LPEI is easy and quick to measure and has very low intraobserver and interobserver variability,[3,17] thus strengthening the validity of the difference observed between baseline and pre-discharge. Moreover, LPEI is obtained with pulsed-Doppler and is therefore vendor-independent.

LPEI is equal to the electromechanical delay (corresponding to excitation–contraction coupling) plus isovolumic contraction time. LPEI is correlated with LVEF, dP/dt$_{max}$, global longitudinal strain, and stroke volume.[17] A normal ventricle has a short LPEI whereas an abnormal ventricle (such as in heart failure) has a long LPEI. LPEI can be considered a good maker of global systolic function and therefore a decrease of LPEI is indicative of improved systolic function. Cazeau *et al.* studied 18 parameters of dyssynchrony and showed

that LPEI was the one correlated with the greatest number of other parameters, 13 out of 17.[18] A decrease of LPEI was associated with directionally similar changes of the other parameters indicating improved synchrony. We found that a 16 ms decrease in LPEI was the optimal cut-off for predicting CRT response at 6 months. In a previous pilot study,[11] a strategy of CRT implantation aiming at reducing LPEI by at least 10 ms (by repositioning the right ventricular lead and if necessary, adding a second right ventricular lead) was acutely associated with an improved diastolic filling duration, an interventricular delay reduction, and an increase in LVEF. The present study suggests that a greater reduction in LPEI might be required to observe CRT response at 6 months.

Finally, our study is in line with the well-known fact that ischemic cardiomyopathy is associated with a lower likelihood of LV reverse remodelling after CRT.[19,20] In our study, the aetiology of heart failure was the second independent factor of CRT response. Patients with non-ischemic cardiomyopathy and with a delta LPEI above the cut-off value of 16 ms had a very high response rate (85%) while patients with ischemic cardiomyopathy and a poor LPEI reduction had a very low likelihood of response (36%).

Study limitations

The number of patients and the follow-up duration limited to 6 months are the main limitations of this study. There were few deaths and hospitalizations for heart failure, and the CRT response was mainly driven by LV reverse remodelling.

Other dyssynchrony parameters were not studied, and perhaps a combination of parameters might have a better prediction capability than any parameter considered alone. A relatively high proportion of patients with atrial fibrillation was included, precluding conclusions regarding atrioventricular dyssynchrony. Finally, atrioventricular and interventricular delays optimization was not performed, and this might also influence response to CRT.

Conclusions

In a standard CRT population, acute correction of intraventricular electromechanical dyssynchrony evaluated by a simple parameter, the LPEI, predicted CRT response at 6 months.

Conflicts of interest

Dr. Anselme reports speaker and consulting fees from Boston Scientific, Medtronic, and MicroPort. Drs. Moubarak and Viart declare no conflicts of interest.

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