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Clinical Research

# Clinical Significance of Electromechanical Dyssynchrony and QRS Narrowing in Patients With Heart Failure Receiving Cardiac Resynchronization Therapy

Ludovic Appert, MD,[a] Aymeric Menet, MD, PhD,[a] Alexandre Altes, MD,[a] Pierre Vladimir Ennezat, MD, PhD,[b] Hélène Bardet-Bouchery, MD,[a,c] Camille Binda, MD,[a] Yves Guyomar, MD,[a] François Delelis, MD,[a] Anne-Laure Castel, MD,[a] Caroline Le Goffic, MD,[a] Raphaelle-Ashley Guerbaai, RN,[b,d] Pierre Graux, MD,[a] Christophe Tribouilloy, MD, PhD,[e,f] and Sylvestre Maréchaux, MD, PhD[a,f]

[a] *GCS-Groupement des hôpitaux de l'institut Catholique de Lille, Cardiology Department, Université Catholique de Lille, Lille, France*

[b] *Cardiology Department, Centre Hospitalier Universitaire de Grenoble, Grenoble, France*

[c] *Centre Hospitalier de la Région de Saint Omer, Saint Omer, France*

[d] *Department of Public Health, University of Basel, Basel, Switzerland*

[e] *Cardiology Department, Centre Hospitalier Universitaire d'Amiens, Amiens, France*

[f] *Laboratoire UPJCV, Université de Picardie, Amiens, France*

***See editorial by Terricabras and Khaykin, pages 12–14 of this issue.***

## ABSTRACT

**Background:** We hypothesized that preoperative electromechanical dyssynchrony amenable to cardiac resynchronization therapy (CRT) and QRS narrowing immediately after CRT are both correlated and have a cumulative impact on response and outcome after CRT.

**Methods:** A total of 233 CRT candidates (heart failure New York Heart Association classes II-IV, ejection fraction $<$ 35%, QRS $\geq$ 120 milliseconds, 44% women, 71 $\pm$ 11 years old) were prospectively included. Preoperative electromechanical dyssynchrony amenable to CRT was assessed by septal deformation patterns using speckle tracking echocardiography. QRS narrowing was calculated from 12-lead electrocardiograms before and immediately after CRT implantation. The primary endpoint was overall mortality during long-term follow-up. The NTC clinical trial number is NCT02986633.

## RÉSUMÉ

**Contexte :** Notre hypothèse était que l'asynchronisme électromécanique préopératoire pouvant bénéficier d'une thérapie de resynchronisation cardiaque (TRC) et que le rétrécissement du complexe QRS immédiatement après la TRC sont corrélés et ont des effets cumulatifs sur la réponse à la TRC et sur l'issue de cette intervention.

**Méthodes :** Au total, 233 patients candidats à une TRC (insuffisance cardiaque de classe II à IV de la New York Heart Association, fraction d'éjection $<$ 35 %, QRS $\geq$ 120 millisecondes, 44 % de femmes, âge moyen 71 $\pm$ 11 ans) ont été inclus de façon prospective. L'asynchronisme électromécanique préopératoire pouvant bénéficier d'une TRC a été évalué par l'étude de la déformation du septum par échocardiographie à suivi de pixel. Le rétrécissement du complexe QRS a été mesuré par électrocardiographie à 12 dérivations avant et

Cardiac resynchronization therapy (CRT) is a recognized treatment for patients with heart failure (HF), impaired left ventricular (LV) function, and increased QRS duration.[1] The absence of QRS narrowing after CRT is associated with lesser improvement of cardiac function and functional status compared with patients with CRT-mediated QRS narrowing.[2] In addition, lack of QRS narrowing after CRT is also associated with a nearly 3-fold increased risk of mortality after CRT.[3]

The relationship between mechanical dyssynchrony assessed by echocardiography, response to CRT, and outcome needs further investigation.[4] Electromechanical dyssynchrony is defined by a left bundle branch block (LBBB)-like contractile activation delay, with an early presystolic septal motion and a late postsystolic contraction of the posterolateral wall.[5,6] Electromechanical dyssynchrony can be assessed using conventional echocardiographic techniques (M-mode or

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Corresponding author: Dr Sylvestre Maréchaux, Cardiology Department, Hôpital Saint Philibert, 115 rue du Grand But, 59462 Lomme Cedex, France. Tel.: +33-320225057; fax: +33-32005608.

E-mail: sylvestre.marechaux@gmail.com

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**Results:** Eighty-seven percent of patients with preoperative electromechanical dyssynchrony experienced QRS narrowing after CRT (118/136), whereas 69% of patients without preoperative electromechanical dyssynchrony (67/97) experienced QRS narrowing after CRT ($P < 0.001$). By Cox multivariate analysis, both preoperative electromechanical dyssynchrony and lack of postoperative QRS narrowing were independently associated with an increased risk of mortality during follow-up (adjusted hazards ratio [HR] 2.24, 95% confidence interval [CI] 1.43-3.50 and HR 1.90, 95% CI 1.06-3.38, respectively). Compared with patients with preoperative electromechanical dyssynchrony, patients without both electromechanical dyssynchrony and postoperative QRS narrowing experienced a considerable increased risk of mortality during follow-up (adjusted HR 3.70, 95% CI 1.96-6.97).

**Conclusions:** Lack of postoperative QRS narrowing after CRT is associated with preoperative electromechanical dyssynchrony. Both preoperative electromechanical dyssynchrony and postoperative QRS narrowing have a favourable cumulative impact on outcome after CRT.

immédiatement après la pose du stimulateur. Le paramètre d'évaluation principal était la mortalité globale au cours du suivi à long terme. Le numéro d'essai clinique NTC de cette étude est **NCT02986633**.

**Résultats :** Un rétrécissement du complexe QRS après la TRC a été observé chez 87 % (118/136) des patients qui présentaient un asynchronisme électromécanique préopératoire, comparativement à 69 % des patients (67/97) ne présentant pas ce trouble ($p < 0{,}001$). Par une analyse multivariée selon le modèle de Cox, tant l'asynchronisme électromécanique préopératoire que l'absence de rétrécissement postopératoire du complexe QRS étaient associés de façon indépendante à une augmentation du risque de mortalité durant la période de suivi (rapport des risques instantanés ajusté [RRI], 2,24; intervalle de confiance [IC] à 95 %, 1,43-3,50 et RRI 1,90; IC à 95 % 1,06-3,38, respectivement). Comparativement aux patients présentant un asynchronisme électromécanique préopératoire, ceux qui ne présentaient ni asynchronisme électromécanique ni rétrécissement postopératoire du complexe QRS ont été exposés à un risque considérablement accru de mortalité pendant la période de suivi (RRI ajusté, 3,70; IC à 95 %, 1,96-6,97).

**Conclusions :** L'absence de rétrécissement postopératoire du complexe QRS après une TRC est associée à un asynchronisme électromécanique préopératoire. Tant l'asynchronisme électromécanique préopératoire que le rétrécissement postopératoire du complexe QRS ont une incidence cumulative favorable sur l'issue de la RC.

bidimensional) by the visual identification of a septal flash or LV apical rocking. Speckle-tracking imaging allows the assessment of myocardial strain based on the tracking of acoustic markers ("speckles") in gray-scale echocardiographic images.[7] Speckles can be tracked from frame to frame, hence allowing strain calculation. Parameters derived from speckle tracking strain, including the identification of an LBBB-like activation of the left ventricle by speckle tracking strain or the characterization of septal deformation strain patterns, refine the assessment of electromechanical echocardiographic indices of dyssynchrony amenable to CRT.[5,8,9]

Previous reports have highlighted the strong relationship between electromechanical dyssynchrony indices, haemodynamic response to CRT, and an excellent long-term outcome after CRT.[10,11]

Thus, we hypothesized that postoperative QRS narrowing after CRT may be linked to the underlying preoperative electromechanical dyssynchrony. The prognostic impact of postoperative QRS narrowing according to preoperative electromechanical dyssynchrony was subsequently investigated, with the hypothesis that lack of QRS narrowing in patients without preoperative electromechanical dyssynchrony amenable to CRT predicts a low rate of CRT response and a poor outcome.

## Methods

### Study population

Two hundred and thirty-three ambulatory patients with HF referred to our institution for CRT device implantation between 2010 and 2014 were enrolled in the present study. Indications for CRT were LV ejection fraction $\leq$ 35% and New York Heart Association (NYHA) class II, III, and ambulatory IV despite optimal medical treatment, with the QRS duration of 120 milliseconds or more in patients with LBBB morphology or with the QRS duration of 150 milliseconds or more in patients with a non-LBBB morphology. Exclusion criteria were: (1) recent (< 3 months) acute coronary syndrome or coronary revascularization, (2) primary mitral or aortic valve disease, and (3) rapid uncontrolled atrial fibrillation. Patients were treated with β-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and spironolactone, as indicated by current guidelines. The study was approved by our institutional review board (Lille Catholic University ethics committee for noninterventional research). Informed consent was obtained for all patients. The NTC clinical trial number is NCT02986633.

### CRT device implantation

Medtronic (Minneapolis, MN), Boston Scientific (Natick, MA), St. Jude Medical (St Paul, MN), Biotronik (Berlin, Germany), and Sorin (Milan, Italy) CRT devices were implanted as previously reported.[9] Interventricular timing was set at zero. A short-sensed atrioventricular delay and a paced delay (80-100 milliseconds and 130 milliseconds, respectively) were programmed to promote biventricular pacing. The absence of fusion or pseudofusion beats on the electrocardiogram (ECG) was verified on continuous monitoring before hospital discharge. In case of ongoing atrial fibrillation and if sufficient bradycardia was not obtained with optimal medical treatment, radiofrequency ablation of the atrioventricular node was performed to promote biventricular pacing. In this case, devices were programmed in a VVIR pacing mode with a heart rate of 70 beats/min.

## Electrocardiogram

Twelve-lead ECG was performed 1 day before and 1 day after the procedure of CRT implantation. Measurements were offline performed with millimeter paper by an investigator (HBB) blinded to the patient's clinical and outcome data. QRS duration before and after CRT implantation was assessed from the earliest QRS onset to the latest offset in any of the leads before and after implantation to obtain the wider QRS, with the beginning of the paced QRS corresponding to the stimulation spike. Relative QRS narrowing (ΔQRS%) was the subtraction of the postoperative and the preoperative QRS duration divided by the preoperative QRS duration. Patients were classified into 2 groups: those with QRS narrowing ($\Delta$QRS% $< 0$, QRS narrowing [+]) and those without ($\Delta$QRS% $\geq 0$, QRS narrowing [−]). Interobserver variability of both preoperative and postoperative QRS duration was previously reported in our institution.

## Echocardiography

Echocardiography was performed 1 day before CRT device implantation and at 9-month follow-up by 1 investigator unaware of the clinical status of the patient using a Vivid E9 ultrasound system (General Electric Healthcare, Velizy, France). Akinetic or dyskinetic segments with a local wall thinning and hyperreflectivity in comparison with adjacent contractile segments were considered as "scarred." Standard echocardiographic measurements were performed according to the European Association of Cardiovascular Imaging guidelines. Strain analysis was performed on apical views recorded at frame rates of 55 to 90 frames/s. Longitudinal 2-dimensional speckle tracking strain analysis was performed offline using a dedicated workstation (EchoPAC PC release BT11; GE Vingmed US, Velizy, France). Aortic valve opening and closure onset were determined using LV outflow tract Doppler recordings. Automatic tracking of the endocardium on an end-systolic frame was checked. The region of interest was then manually modified to obtain an optimal tracking and to cover the whole thickness of the LV myocardium. Global longitudinal strain was obtained by averaging longitudinal strain from the 3 apical views.

The septal shortening and stretching sequence was used to classify septal deformation patterns as previously reported.[9,12] Three patterns were characterized: (1) pattern 1: double-peaked systolic shortening; (2) pattern 2: early pre-ejection shortening peak followed by prominent systolic stretch; (3) pattern 3: pseudonormal shortening with late systolic shortening peak, no or minimal pre-ejection lengthening, and less pronounced end-systolic stretch. Patterns 1 and 2 were previously associated with a high probability of CRT response and a favourable outcome, whereas pattern 3 was not.[9,11] Patients with a pattern 1 or 2 were considered having electromechanical dyssynchrony amenable to CRT. Septal strain tracing and pattern recognition were performed by investigators blinded to the patient's clinical and follow-up data.

The change in LV end-systolic volume (ΔLVESV) was defined as the reduction in LVESV between baseline and 9-month follow-up relative to baseline LVESV. Response to CRT was defined as ΔLVESV $\geq$ 15%. The interobserver reproducibility of ΔLVESV after CRT in our echocardiography laboratory is fair, with an intraclass correlation coefficient of 0.91.[3]

## Outcomes

During follow-up, patients were monitored by their own private physicians. Clinical events were recorded by clinical interviews and/or by phone calls to physicians, patients, and next of kin (if necessary). The primary endpoint of the study was overall mortality. Cardiovascular mortality was considered if death was related to HF, myocardial infarction, arrhythmia, or sudden death. Clinical response to CRT was defined as an improvement in at least 1 NYHA functional class at 9-month follow-up.

## Statistical analysis

Quantitative data are presented as mean ± standard deviation or median [25th-75th percentile]. Qualitative data are presented as percentages. Comparison of the means was carried out using a paired 2-sided Student's *t*-test or Mann-Whitney *U* test as appropriate. Continuous variables for different groups of patients were compared using 1-way analysis of variance or the Kruskall-Wallis test as appropriate. Comparison of categorical variables was carried out using a $\chi^2$test or a Fisher's exact test as appropriate. The duration of follow-up was computed for each endpoint using the reverse Kaplan-Meier method. Survival curves using categorical variables were obtained using the Kaplan-Meier method. Multivariate Cox regression survival analyses were used to identify the relationship between septal deformation patterns, postoperative QRS narrowing, and mortality during follow-up. The proportional hazard assumption was confirmed using statistics and graphs on the basis of Schoenfeld residuals. For both multivariate Cox analyses, model building techniques were not used and covariates entered in the model were considered for potential prognostic impact, on an epidemiologic basis. These covariates included preoperative QRS duration, NYHA functional class III or IV, age, coronary artery disease, serum creatinine serum levels, LBBB, and LV ejection fraction (%). Hazard ratios (HRs) for continuous variables in Cox models were rescaled by the within-study standard deviation. Multivariate logistic regression analysis models were built to investigate the relationship between preoperative septal deformation patterns, postoperative QRS narrowing, and clinical response to CRT. As for survival analysis, model building techniques were not used and covariates entered in the model were considered as classically associated with response to CRT on an epidemiologic basis.[13] These covariates included preoperative QRS duration, female sex, LBBB, atrial fibrillation, coronary artery disease, and amount of myocardial scar. For all tests, a 2-tailed *P* value $\leq 0.05$ was considered statistically significant. Statistical analysis was performed with R 3.0.3 (Youngstown, OH).

# Results

## Baseline characteristics

The study population included 233 patients (44% women, mean age 71 ± 11 years) with HF and LV systolic dysfunction despite optimal medical treatment. All patients received CRT (79% of them with an implantable cardioverter defibrillator). Half of the study population were in NYHA

**Table 1. Clinical and echocardiographic data according to a septal deformation pattern 1/2 vs 3 and lack or presence of QRS narrowing (QRS↓ (−) and QRS↓ (+), respectively)**

| Variable | All N = 233 | Septal pattern 1/2 QRS↓ (+) N = 118 | Septal pattern 1/2 QRS↓ (−) N = 18 | Septal pattern 3 QRS↓ (+) N = 67 | Septal pattern 3 QRS↓ (−) N = 30 | *P* value |
|---|---|---|---|---|---|---|
| Age (y) | 71 ± 11 | 72 ± 11 | 65 ± 14 | 74 ± 11 | 70 ± 11 | **0.029** |
| Male sex (%) | 66 | 57 | 89 | 72 | 77* | **0.010** |
| BMI (kg/m$^2$) | 27 ± 5 | 27 ± 6 | 26 ± 3 | 28 ± 5 | 28 ± 5 | 0.765 |
| ICD (%) | 79 | 76 | 89 | 79 | 87 | 0.450 |
| Diabetes (%) | 28 | 31 | 22 | 25 | 30 | 0.820 |
| Dyslipidemia (%) | 41 | 42 | 29 | 43 | 33 | 0.599 |
| Coronary artery disease (%) | 37 | 32 | 28 | 40 | 53 | 0.135 |
| Atrial fibrillation (%) | 24 | 19 | 17 | 27 | 37 | 0.187 |
| NYHA functional classes III-IV (%) | 51 | 48 | 44 | 58 | 47 | 0.525 |
| Heart rate (bpm) | 72 ± 14 | 74 ± 14 | 76 ± 12 | 70 ± 12 | 71 ± 16 | 0.182 |
| Systolic blood pressure (mm Hg) | 123 ± 20 | 124 ± 19 | 120 ± 25 | 123 ± 21 | 118 ± 21 | 0.633 |
| Diastolic blood pressure (mm Hg) | 69 ± 12 | 70 ± 12 | 68 ± 12 | 69 ± 11 | 67 ± 11 | 0.579 |
| Baseline QRS width (ms) | 164 ± 26 | 170 ± 22 | 144 ± 20 | 170 ± 29 | 141 ± 17* | **< 0.001** |
| Left bundle branch block (%) | 78 | 80 | 94 | 72 | 77 | 0.201 |
| RV pacing (%) | 13 | 15 | 0 | 15 | 7 | 0.211 |
| β-Blockers (%) | 89 | 86 | 89 | 91 | 93 | 0.680 |
| Renin angiotensin antagonists (%) | 87 | 86 | 94 | 91 | 83 | 0.519 |
| Creatinine (mg/L) | 13.0 ± 5.8 | 12.6 ± 6.4 | 12.4 ± 5.3 | 13.0 ± 4.5 | 14.4 ± 6.0 | 0.496 |
| LV ejection fraction (%) | 26 ± 5 | 26 ± 5 | 26 ± 5 | 27 ± 6 | 26 ± 5 | 0.873 |
| LV end-diastolic diameter (mm) | 66 ± 8 | 66 ± 9 | 71 ± 5 | 65 ± 8 | 69 ± 7 | **0.019** |
| LV end-diastolic volume (mL) | 245 ± 71 | 241 ± 73 | 285 ± 59 | 234 ± 63 | 258 ± 81 | **0.030** |
| LV end-systolic volume (mL) | 182 ± 60 | 179 ± 59 | 211 ± 52 | 173 ± 53 | 195 ± 74 | 0.053 |
| Global longitudinal strain (%) | −7.99 ± 2.81 | −7.96 ± 2.77 | −7.07 ± 2.74 | −8.58 ± 2.98 | −7.35 ± 2.43 | 0.092 |
| Mitral ERO-A (mm$^2$) | 5 ± 7 | 4 ± 7 | 5 ± 7 | 5 ± 7 | 5 ± 7 | 0.934 |
| Tricuspid annular plane systolic excursion (mm) | 20 ± 5 | 21 ± 5 | 21 ± 6 | 19 ± 5 | 17 ± 5* | **0.001** |
| sPAP (mm Hg) | 38 ± 14 | 37 ± 13 | 36 ± 15 | 41 ± 16 | 39 ± 13 | 0.389 |
| Scarred segments (%) | 15 | 7 | 17 | 21 | 30* | **0.003** |

BMI, body mass index; ERO-A, effective regurgitant orifice area; ICD, implantable cardioverter defibrillator; LV, left ventricular; NYHA, New York Heart Association; RV, right ventricular; sPAP, systolic pulmonary artery pressure.

* $P < 0.05$ vs septal pattern 1/2 QRS↓ (+).

functional class III or IV. The mean QRS width before CRT was 164 ± 26 milliseconds. The characteristics of the study population are depicted in Table 1.

One hundred and thirty-six patients had electromechanical dyssynchrony amenable to CRT as demonstrated by the presence of a septal deformation pattern 1 or 2, whereas 97 patients had a septal deformation pattern 3. QRS narrowing after CRT occurred in 185 patients (79% of the global population).

As shown in Figure 1, 118 of 136 patients (87%) with a septal deformation pattern 1 or 2 experienced QRS narrowing after CRT (88% and 86%, respectively), whereas only 69% of patients with a septal pattern 3 (67/97) experienced QRS narrowing after CRT ($P < 0.001$). Among the 81 patients with a septal deformation pattern 1, only 10 did not experience QRS narrowing. Similarly, among the 55 patients with a septal deformation pattern 2, only 8 did not experience QRS narrowing. The baseline and clinical preoperative characteristics according to preoperative septal deformation patterns and postoperative QRS narrowing are detailed in Table 1. Compared with patients with a septal deformation pattern 1 or 2 and QRS narrowing after CRT, patients with a septal deformation pattern 3 without postoperative QRS narrowing were more frequently male, and had at baseline a lower QRS duration, a lower tricuspid annular plane systolic excursion, and a higher amount of myocardial scar.

## Outcome

Death status was available for all participants. During a median 48-month follow-up, 89 patients died. Fifty-six patients died of cardiovascular causes. As presented in Figure 2A, survival free from all-cause mortality at 1, 2, and 5 years was respectively 93% ± 2%, 88% ± 3%, 74% ± 4% in patients

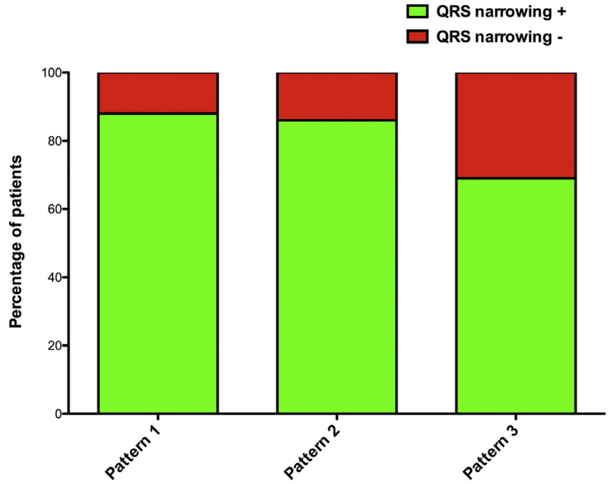


**Figure 1.** Percentage of patients experiencing lack of QRS narrowing according to septal deformation patterns.

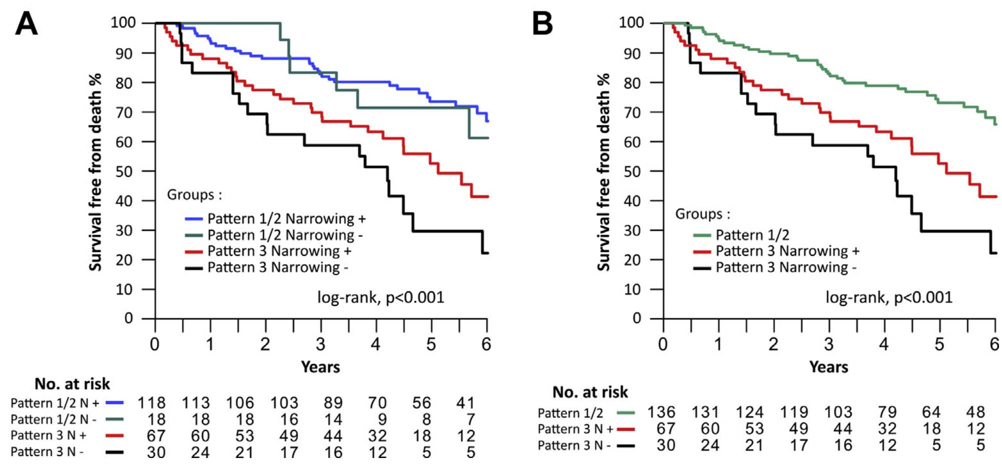


**Figure 2.** (**A**) Survival free from death according to a septal deformation pattern 1/2 vs pattern 3 and the presence or lack of QRS narrowing. (**B**) Survival free from death according to a septal deformation pattern 1/2 vs patients with a septal deformation pattern 3 stratified according to the presence or lack of QRS narrowing.

with pattern 1 or 2 with postoperative QRS narrowing and 100%, 100%, 71% ± 11% in patients with pattern 1 or 2 and without postoperative QRS narrowing, respectively. Survival free from all-cause mortality at 1, 2, and 5 years was respectively 88% ± 4%, 78% ± 5%, 53% ± 7% in patients with pattern 3 with postoperative QRS narrowing and 83% ± 7%, 69% ± 9%, 30% ± 10% in patients with pattern 3 without postoperative QRS narrowing, respectively. Overall, all-cause mortality was different between the 4 groups of patients ($P < 0.001$, Fig. 2A) but was similar between patients with pattern 1 or 2 with or without postoperative QRS narrowing ($P = 0.48$). Hence, 5-year survival free from overall mortality, in patients with a septal pattern 1 or 2 (73% ± 4%) compared with patients with pattern 3 with (53% ± 7%) and without (30% ± 10%) postoperative QRS narrowing, is represented in Figure 2B. Compared with patients with pattern 1 or 2, patients with a septal pattern 3 with and without postoperative QRS narrowing experienced a significant increased risk of mortality ($P = 0.0006$ and $P = 0.000001$). By Cox multivariate analysis, both preoperative septal deformation pattern 3 and the absence of postoperative QRS narrowing were independently associated with an increased risk of mortality during follow-up (adjusted HR 2.24, 95% confidence interval [CI] 1.43-3.50 and adjusted HR 1.90, 95% CI 1.06-3.38; Table 2). Compared with patients with a septal deformation pattern 1 or 2, patients with a septal deformation pattern 3 with postoperative QRS narrowing experienced an HR 2.11, 95% CI (1.31-3.42) adjusted increased risk of mortality, whereas those with a septal deformation pattern 3 without postoperative QRS narrowing experienced an HR 3.70, 95% CI (1.96-6.97) increased risk of mortality during follow-up (Table 3).

As presented in Figure 3, patients with a septal deformation pattern 3 with and without postoperative QRS narrowing experienced a significant increased risk of cardiovascular mortality during follow-up compared with patients with a septal deformation pattern 1 or 2. By Cox multivariate analysis, both preoperative septal deformation pattern 3 and lack of postoperative QRS narrowing were independently associated with an increased risk of cardiovascular mortality during follow-up (adjusted HR 3.12, 95% CI 1.70-5.73 and adjusted HR 2.45, 95% CI 1.20-5.01; Table 2). Compared with patients with a septal deformation pattern 1 or 2, patients with a septal deformation pattern 3 with postoperative QRS

**Table 2.** Results of multivariate Cox models including both septal deformation patterns and lack of QRS narrowing with all-cause and cardiovascular mortality as outcomes

| | All-cause mortality | | Cardiovascular mortality | |
|---|---|---|---|---|
| Variable | Adjusted hazard ratio | *P* value | Adjusted hazard ratio | *P* value |
| Septal deformation pattern 3 vs 1/2 | 2.24 (1.43-3.50) | < 0.001 | 3.12 (1.70-5.73) | < 0.001 |
| Lack of QRS narrowing | 1.9 (1.06-3.38) | 0.029 | 2.45 (1.20-5.01) | 0.014 |
| Age (per SD increase) | 1.58 (1.20-2.09) | 0.001 | 1.56 (1.10-2.22) | 0.013 |
| Coronary artery disease | 1.09 (0.70-1.71) | 0.690 | 0.85 (0.46-1.55) | 0.590 |
| NYHA functional classes III-IV | 1.95 (1.21-3.12) | 0.006 | 2.06 (1.13-3.75) | 0.018 |
| Baseline QRS width (per SD increase) | 1.08 (0.87-1.34) | 0.475 | 1.13 (0.87-1.48) | 0.345 |
| Left bundle branch block | 0.94 (0.57-1.55) | 0.810 | 1.19 (0.60-2.36) | 0.614 |
| Creatinine (per SD increase) | 1.42 (1.21-1.66) | < 0.001 | 1.48 (1.23-1.78) | < 0.001 |
| LV ejection fraction (per SD increase) | 0.75 (0.60-0.94) | 0.011 | 0.66 (0.50-0.88) | 0.004 |
| Bayesian information criteria | 862 | | 512 | |
| $R^2$ | 0.288 | | 0.239 | |
| Harell's C statistic | 0.751 | | 0.798 | |

LV, left ventricular; NYHA, New York Heart Association; SD, standard deviation.

**Table 3. Results of multivariate Cox models comparing the combination of a septal deformation pattern 3 and postoperative QRS narrowing (QRS↓ [+] or [−]) with a septal deformation pattern 1/2 as the reference group, with all-cause and cardiovascular mortality as outcomes**

| | All-cause mortality | | Cardiovascular mortality | |
|---|---|---|---|---|
| Variable | Adjusted hazard ratio | *P* value | Adjusted hazard ratio | *P* value |
| Septal deformation pattern 1/2 | Reference | | Reference | |
| Septal pattern 3 QRS↓ (+) | 2.11 (1.31-3.42) | 0.002 | 2.81 (1.45-5.42) | 0.002 |
| Septal pattern 3 QRS↓ (−) | 3.70 (1.96-6.97) | < 0.001 | 6.27 (2.78-14.15) | < 0.001 |
| Age (per SD increase) | 1.55 (1.17-2.04) | 0.002 | 1.5 (1.06-2.14) | 0.024 |
| Coronary artery disease | 1.11 (0.71-1.73) | 0.653 | 0.85 (0.46-1.58) | 0.615 |
| NYHA functional classes III-IV | 1.95 (1.21-3.13) | 0.006 | 2.08 (1.14-3.8) | 0.018 |
| Baseline QRS width (per SD increase) | 1.04 (0.84-1.3) | 0.701 | 1.09 (0.83-1.42) | 0.534 |
| Left bundle branch block | 0.94 (0.57-1.54) | 0.797 | 1.21 (0.61-2.39) | 0.592 |
| Creatinine (per SD increase) | 1.43 (1.22-1.67) | < 0.001 | 1.48 (1.23-1.78) | < 0.001 |
| LV ejection fraction (per SD increase) | 0.75 (0.6-0.93) | 0.010 | 0.65 (0.49-0.87) | 0.004 |
| Bayesian information criteria | 864 | | 514 | |
| $R^2$ | 0.282 | | 0.232 | |
| Harell's C statistic | 0.749 | | 0.792 | |

LV, left ventricular; NYHA, New York Heart Association; SD, standard deviation.

narrowing experienced an HR 2.81, 95% CI (1.45-5.42) adjusted increased risk of cardiovascular mortality, whereas those with a septal deformation pattern 3 without postoperative QRS narrowing experienced an HR 6.27 95% CI (2.78-14.15) increased risk of cardiovascular mortality during follow-up (Table 3).

## Echocardiographic and clinical response to CRT

A follow-up echocardiogram was performed in 204 patients at 9-month follow-up (88% of the study population). Clinical response was observed in the vast majority of these patients (89%). However, the proportion of patients with clinical response to CRT was not significantly different between the study subgroups of patients defined by septal deformation patterns and lack of QRS narrowing ($P = 0.15$). Overall, 75% of patients were echocardiographic responders to CRT. The relationship between response to CRT, preoperative septal deformation patterns, and postoperative QRS narrowing is depicted in Figure 4. The rate of responders to CRT tended to be lower in patients with a septal deformation pattern 1 or 2 without postoperative QRS narrowing compared with those with pattern 1 or 2 and QRS narrowing, but the difference did not reach statistical significance (70% vs 88%, $P = 0.13$). By multivariate logistic regression including classical factors associated with CRT response, septal deformation pattern 1 or 2 and QRS narrowing were both associated with CRT response (adjusted odds ratio 8.81, 95% CI 3.84-20.22 and odds ratio 4.21, 95% CI 1.59-11.15, respectively). Overall, 92% of patients with a septal deformation pattern 1 or 2 experienced CRT response (Fig. 4). The CRT response rate was 51% in patients with pattern 3. Among patients with a septal deformation pattern 3, those with postoperative QRS narrowing had a CRT response rate of 63%, whereas those with lack of postoperative QRS narrowing were CRT responders in only 23% of cases.

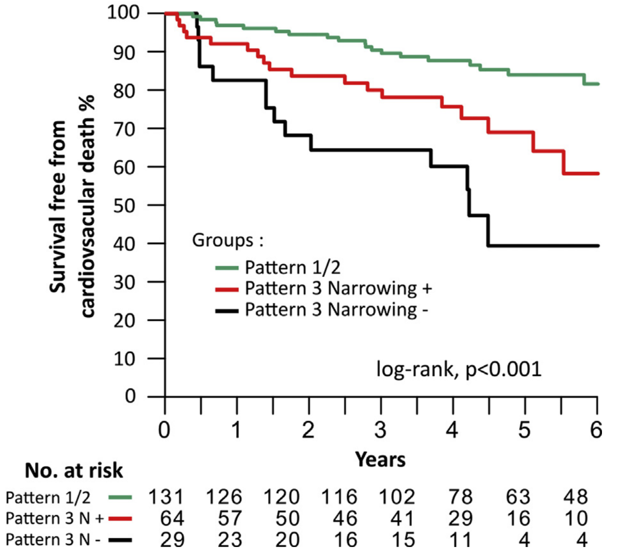


**Figure 3.** Survival free from cardiovascular death according to a septal deformation pattern 1/2 vs patients with a septal deformation pattern 3 stratified according to the presence or lack of QRS narrowing.

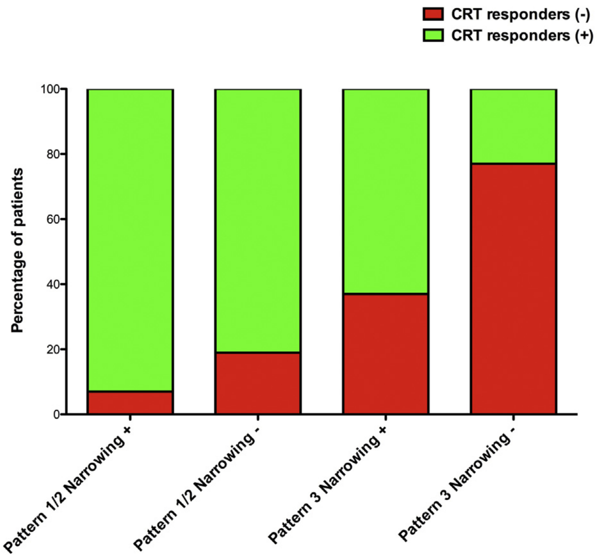


**Figure 4.** Percentage of cardiac resynchronization therapy (CRT) responders according to septal deformation patterns and the presence or lack of QRS narrowing.

## Discussion

The present data indicate that preoperative electromechanical dyssynchrony amenable to CRT and postoperative QRS narrowing are both important determinants of LV response and outcome after CRT. Although most patients with electromechanical dyssynchrony amenable to CRT assessed by echocardiography will experience postoperative narrowing and will respond to CRT, lack of QRS narrowing will be encountered in nearly one-third of patients without preoperative electromechanical dyssynchrony amenable to CRT, that is, pattern 3. This leads to a very low response rate to CRT and a poor outcome. Thus, the present data indicate that preoperative echocardiographic assessment of dyssynchrony amenable to CRT is only 1 determinant of response and outcome after CRT; postoperative factors including quality of resynchronization as assessed by QRS narrowing on ECG play an important role. However, QRS narrowing seems to be at least in part determined by preoperative electromechanical dyssynchrony. Patients without electromechanical dyssynchrony amenable to CRT who do not experience immediate postoperative QRS narrowing represent a very high risk group, who will not experience CRT response in most cases during follow-up. Hence, the present study demonstrates that the combination of preoperative echocardiography and postoperative ECG data refines the prediction of outcome and response after CRT.

The assessment of delays between LV walls to assess myocardial dyssynchrony has not been consistently associated with response to CRT in multicentre studies.[4] Indeed, contractile delays between LV walls depends not only on electrical abnormalities but also on other important factors including loading conditions and amount of myocardial scar.[14] In contrast, the assessment of electromechanical dyssynchrony based on a mechanical approach seems more promising. In the normal heart without conduction abnormalities, electrical activation starts within the LV and right ventricular (RV) endocardium. In case of a complete LBBB, electrical activation starts in the right ventricle and proceeds across the interventricular septum for 40 to 50 milliseconds before reaching the LV endocardium. The electrical activation then re-enters into the Purkinje network and propagates to the LV posterolateral wall endocardium; 50 additional milliseconds are thus required. The activation of the posterolateral wall requires another 50 milliseconds, thereby producing a total QRS duration of 140 to 150 milliseconds. LBBB is identified by an early deformation of the septum owing to the contraction of the right ventricle free wall. This early deformation of the RV free wall is unopposed, as the contraction of the LV posterolateral wall is delayed owing to the conduction delay. A counter wall motion toward the right ventricle of the interventricular septum, resulting from the vigorous contraction of the LV free wall, follows this early movement. This movement can be detected visually, using M-mode and/or tissue Doppler imaging (the septal flash) or using speckle tracking strain imaging (LV classical LBBB activation pattern).[5,14] The movement of the LV septal wall deformation has been particularly well described using speckle tracking strain.[9,12] Briefly, patients with a prominent early septal deformation assessed by speckle tracking strain (who are those with a septal pattern 1 or 2) have a high response rate after CRT.[9] This early abnormal motion of the septum is consequently followed by a clockwise motion of the apex named "apical rocking."[15] The patients with these typical LV contractile abnormalities as a consequence of the LV activation have larger baseline QRS duration, have more frequently an LBBB on the ECG, have a lesser amount of myocardial scaring, and a lower rate of coronary artery disease.[10] However, these LV contractile abnormalities can be found in patients with intermediate QRS duration or in patients with a nonclassical LBBB configuration on the ECG.[6] These patients with "electromechanical dyssynchrony" have a very high rate of response to CRT.[5] In contrast, patients without electromechanical dyssynchrony have a lower CRT response rate and a lower survival after CRT. Hence, preoperative electromechanical dyssynchrony assessed by this approach is an important determinant of the response after CRT, indicating that this approach identifies dyssynchrony amenable to CRT. However, around half of patients without electromechanical dyssynchrony (ie, those with a septal pattern 3) experience reverse remodelling after CRT, whereas the other half do not.[9] Hence, we hypothesized that other factors but preoperative electromechanical dyssynchrony amenable to CRT may be involved in the response and outcome after CRT.

We previously reported that lack of QRS narrowing after CRT is associated with a decreased CRT response rate and a lower survival after CRT.[2] Hence, QRS narrowing should be considered as an immediate surrogate of the quality of resynchronization. The present study builds on previous reports by demonstrating that lack of QRS narrowing is more commonly found in patients with a septal pattern 3 (31% of patients) and is associated with a very low rate of CRT responders (23%) and a considerable increased risk of mortality. In contrast, lack of QRS narrowing is infrequent in patients with preoperative electromechanical dyssynchrony amenable to CRT, and seems to have a minimal impact on CRT response and outcome in this specific subgroup of patients. Hence, lack of QRS narrowing in patients without preoperative electromechanical dyssynchrony suggests that the myocardial substrate does not permit an efficient resynchronization. One explanation may be that the myocardial disease is too severe in some patients without electromechanical dyssynchrony to achieve this goal, as indicated by more depressed RV function and a higher amount of myocardial scar assessed by echocardiography in the present report. However, the present study clearly also suggests that QRS narrowing should be considered as a goal when placing CRT, especially in those in whom electromechanical dyssynchrony amenable to CRT is not found during the preoperative echocardiogram. Whether CRT should be turned off in these patients when QRS narrowing cannot be achieved cannot be ascertained from the present observational nonrandomized study.

## Limitations

This is a noncontrolled single-centre study. In addition, the present findings reflect the practice of our tertiary center; hence, they may not be generalizable to daily practice. However, the collection of clinical and echocardiographic data was prospective with echocardiographic offline analysis. Patient follow-up was also prospectively planned. In addition, QRS width assessment and septal deformation patterns were performed by cardiologists blinded to clinical, echocardiographic, and outcome data. Cardiac magnetic resonance imaging provides invaluable information regarding LV function and fibrosis of the lateral wall. In addition, the assessment of diffuse fibrosis with particularly the T1 mapping sequences provides important information regarding CRT response. However, cardiac magnetic resonance imaging was not systematically performed in the present study; hence, the scar burden cannot be precisely evaluated. Clinical response was not significantly related to septal deformation patterns and lack of QRS narrowing in the present study. However, previous reports have demonstrated that clinical response assessed by NYHA functional changes, quality of life score, or 6-minute walking distance does not predict long-term survival in contrast to the assessment of reverse remodelling that is less influenced by the placebo effect.[16] QRS narrowing was used as a binary variable, as we previously demonstrated that the relationship between changes in QRS duration and mortality is not linear.[2] Lastly, the prognostic value of septal deformation patterns and the absence of QRS narrowing on top of classical parameters of CRT response needs external validation in a larger multicentre cohort of patients.

## Conclusions

Postoperative QRS narrowing after CRT is linked to preoperative electromechanical dyssynchrony. Lack of postoperative QRS narrowing in patients without preoperative electromechanical dyssynchrony amenable to CRT is associated with a very low rate of CRT response and a considerable increased risk of mortality during follow-up. The findings of the present study highlight (1) the importance of the preoperative assessment of electromechanical dyssynchrony amenable to CRT by echocardiography in patients undergoing CRT and (2) the importance of postoperative assessment of QRS narrowing, especially in those whom the preoperative echocardiogram does not indicate electromechanical dyssynchrony amenable to CRT. Further larger multicentre studies are needed to confirm these findings.

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## Disclosures

The authors declare that they have no relevant conflicts of interest to disclose.

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