Validation of an echocardiographic multiparametric strategy to increase responders patients after cardiac resynchronization: a multicentre study

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Aims
We sought to develop and validate a multiparametric algorithm by applying previously validated criteria to predict cardiac resynchronization therapy (CRT) response in a multicentre study. Thirty per cent of patients treated by CRT fail to respond to the treatment. Although dyssynchrony by echocardiography has been used to improve the selection of patients, the complexity of myocardial contraction has generated a moderate improvement using any of several individual parameters.

Methods and results
Two hundred end-stage heart failure patients [NYHA 3–4 and left ventricular ejection fraction (LVEF), 35%] with QRS > 120 ms were included. Echocardiography analysis focused on the following parameters: atrioventricular dysynchrony, interventricular dyssynchrony, and intraventricular dyssynchrony that integrated radial (PSAX M-mode) and longitudinal [tissue Doppler imaging (TDI)] evaluations for spatial (wall to wall) and temporal (wall end-systole to mitral valve opening) dyssynchrony diagnosis. Following CRT implantation, patients were monitored for 6 months with functional and echo evaluations defining responders by a 15% reduction in end-systolic volume. Mean QRS duration and LVEF were 152 ± 17 ms and 25 ± 8%. There was a CRT response in 57% of patients, independent of QRS width. Mean prevalence of positive criteria was 34 ± 8%. Feasibility and variability averages were 81 ± 20% and 9 ± 4%. In a single parametric approach, ranges of sensitivities and specificities were 18–65% and 45–84% with a mean of 41% and 66%. A multiparametric approach by focusing on criteria combination decreased the mean rate of false-positive results to 14 ± 12%, 5 ± 4%, 2 ± 2%, and 1 ± 2% from one to four parameters, respectively. More than three parameters were associated with a specificity above 90% and a positive predictive value above 65%. Reproducibility of this global strategy was 91%.

Conclusion
A multiparametric echocardiographic strategy based on the association of conventional criteria is a better indicator of CRT response than the existing single parametric approaches.

Keywords
Cardiac resynchronization • Echocardiography • Heart failure
Introduction

Evidence of the clinical benefits of cardiac resynchronization therapy (CRT) is now well documented in several multicentre randomized clinical trials. Based on the substantial body of evidence available, CRT is currently a Class I recommendation in patients with 35% or less left ventricular ejection fraction (LVEF), sinus rhythm, and electrical ventricular dyssynchrony (QRS width \( \geq 120 \text{ ms} \)), who remain symptomatic (NYHA Class III–IV) despite optimal drug treatment. The QRS width is, currently, the approved selection criterion for the implantation of CRT devices. However, \( \sim 30 \% \) of patients do not respond clinically to CRT and 45% show no evidence of reverse remodelling. On the other hand, the presence of mechanical dyssynchrony was documented in patients with narrow QRS demonstrating that asynchronous contraction can be present without substantially increasing the QRS duration on the surface electrocardiogram (EKG). Attempts to identify and quantify mechanical asynchrony directly, rather than relying solely on QRS prolongation, lead to the investigation of the possible role of echocardiography. Using conventional and sophisticated echocardiographic techniques, several echocardiographic parameters have been extensively investigated and some of them have clearly been shown to predict response to CRT. However, the proportion of non-responder patients remains significant in these studies, ranging 10–50%, and is sometimes close to the EKG criteria selection level.

Finally, the results of the PROSPECT study have highlighted the lack of reliability and reproducibility of each independent parameter integrated in a single parametric approach.

In order to improve the number of responder patients based on echocardiographic evaluation, we hypothesized that the combination of several echocardiographic criteria could be linked to a higher level of adequate response. Therefore, we evaluated the systematic combination of 1 to 4 conventional parameters described in the literature in predicting response to CRT. Consequently, we sought to develop and validate a strategy of criteria application to be used in clinical practice.

Methods

Patients and protocol

Two hundred heart failure patients (mean age 67 \( \pm \) 13 years) from three medical centres were included in this study after a decision of the implantation of a CRT device based on current ESC recommendations. Therefore, patients were presented with severe symptomatic heart failure despite optimal pharmacological therapy (NYHA functional Class III or IV); they had evidence of left ventricular (LV) systolic dysfunction with an EF<35%. Patients were included when the QRS duration was above 120 ms independently of the echocardiographic dyssynchrony parameters.

Clinical status (NYHA class) was assessed at baseline and at 6 months follow-up. At 6 months follow-up, the LVEF and LV volumes, severity of mitral regurgitation, diastolic function and pulmonary artery pressures were reassessed by echocardiography. Hospitalization for heart failure and survival were assessed during 6 months follow-up after pacemaker implantation.

Responders to CRT were defined by a reduction of 15% of systolic LV volume measured by conventional echography using Simpson’s method from baseline to 6 months follow-up.

Biventricular device implantation

The LV pacing lead was inserted transvenously via the subclavian route. The LV pacing lead was inserted via the coronary sinus using an 8-F guiding catheter and positioned preferably in a (postero)lateral vein. Otherwise, the LV lead was positioned in the anterior position or in the mid-cardiac vein. The right ventricle lead was positioned at the apex or at the mid-septum at the implantation’s discretion. The atrioventricular delay (but not ventricle to ventricle delay) was optimized by two-dimensional (2D) echocardiography so that it provided the longest filling time for the completion of the end-diastolic filling flow before LV contraction. When a conventional indication for an ICD existed, a combined device was implanted.

Echocardiography

Standard echocardiography, including Doppler studies, was performed (System 7—General Electric Medical System, Horten, Norway). The LV volumes and EF were assessed by biplane Simpson’s equation using the apical four- and two-chamber views. Cardiac output, rate of pressure rise in systole (dP/dt), right pressure, and mid-systolic mitral regurgitation were measured as previously described.

Parameters of dysynchrony were acquired before the implantation as recently published, and consisted briefly of (Figure 1): (1) Atrioventricular dyssynchrony (AVD), obtained by the measurement of filling time on mitral inflow indexed to the relative risk (RR) interval \( \times 13 \) (LV filling time/RR interval ratio) (2) Interventricular dyssynchrony (IVD), obtained by the difference between left and right pre-ejection delay. (3) Intraventricular dyssynchrony:

- In the radial axis (parasternal view)
  - Septal to posterior wall motion delay (SPWMD) corresponding to a LV dyssynchrony in the spatial field (wall to wall) \( \times 14 \)
  - Overlap inferolateral end-systole in M-mode/mitral valve opening, corresponding to a LV dyssynchrony in the temporal field (radial systole–diastolic overlap (RSDO)) \( \times 13 \)
- In the longitudinal axis (A4C, A3C, A2C)
  - Maximum difference time to onset [tissue Doppler imaging (TDI)]—six basal walls [electromechanical delay (EMD)] \( \times 15,16 \)
  - Maximum difference time to peak (TDI)—six basal walls [electrosystolic delay (ESD)] \( \times 15,17,18 \)
  - Aortic pre-ejectional delay [left pre-ejectional delay (LPED)] \( \times 13 \)
  - Overlap anterolateral end-systole in M-mode/mitral valve opening [longitudinal systole–diastolic overlap (LSDO)] \( \times 13 \)

Each parameter was obtained from three consecutive cardiac cycles and was only included in the algorithm of \(< 15 \% \) beat-to-beat variation in order to improve the total procedure reproducibility.

An Echo Core Laboratory (Ultrasound consulting corp.) also independently performed all measurements.

Statistics

For the comparison of the quantitative variables before and after CRT, the Student t-test was used (paired t-test). The clinical and echocardiographic parameters between responders and non-responders were compared by unpaired t-test or Pearson \( \chi^2 \) test where appropriate.
A high concordance between observers was defined for a Kappa value >0.80.

All data were expressed as mean ± standard deviation. A probability value of P < 0.05 was considered statistically significant.

Results

The study group consisted of 181 patients with complete data sets including baseline echocardiography measurements, dysynchrony analysis, and follow-up volume and EF data. Nineteen patients were excluded due to an incomplete data set (9 deaths, 10 incomplete echocardiographies). Mean EF, end-diastolic volume, end-systolic volume, and QRS duration were 25 ± 8%, 198 ± 69 mL, 148 ± 61 mL, 152 ± 17 ms at baseline. Positive echocardiographic response to CRT, defined as a percentage decrease in end-systolic volume ≥15%, was observed in 103 patients, corresponding to a 57% responder rate (Table 1). Non-responders, compared with responders, were more likely to have ischaemic heart disease (69% vs. 54%, P = 0.06), and slightly shorter QRS duration (149 ± 17 ms vs. 155 ± 15 ms, P = 0.11). No difference was observed between the two groups regarding LV morphology or function, or treatment. At 6 months, 76% of our patients demonstrated an improvement in their NYHA functional status, for whom an echographic response was observed in 92%. A significant relation was obtained between the two parameters (P = 0.001). However, a clinical improvement was observed in 63% of morphological non-responders.

Prediction of response based on a mono-parametric evaluation

The feasibility and inter-observer reproducibility of different parameters are summarized in Figure 1. As previously reported, flow Doppler-based parameters were presented with a higher rate of feasibility and reproducibility than M-mode or TDI parameters.

For quantitative parameters, cut-off values determined by ROC curves allowing highest sensitivity and specificity were 40% for AVD, 40 ms for IVD, 132 ms for SPWMD, 60 ms for EMD and 65 ms for ESD, and 150 ms for LPED. Each parameter was then independently evaluated in terms of prediction of CRT response.

Patients with zero criteria

Patients with no echocardiographic parameter accounted for 7.5% of the global population (Table 1) and were characterized by a significantly lower EKG duration compared with patients with at least one parameter (137 ± 8 ms vs. 147 ± 14 ms, P = 0.04). Seventy per cent of those patients had a QRS width below 160 ms and 10/13 (76%) were non-responders, whereas only 4% of responder patients presented with no echocardiographic dysynchrony criteria. Positive predictive value was 28%. χ² test identified a significant relation between the two criteria (responder/non-responder and presence/absence of echocardiographic parameter) (χ² = 4.4; P = 0.036). No other difference was observed between the two groups.
Patients with one criterion

Depending on the parameter, the prevalence of positive criteria was ranked between 21% and 49% (Figure 2). A total of 34 patients (18%) were presented with one isolated parameter, 12/103 in the responders group (12%) vs. 22/78 in the non-responders group (28%). Electrosystolic delay was the most frequently observed parameter (49%) and RSDO the lowest (21%). Specificity and sensitivity averages were $66\pm12\%$ and $41\pm14\%$, respectively (Table 2). The highest specificity for predicting a good response rate was 84% for the EMD parameters, but was observed in only 27% of our population. Regarding the PPV of each parameter, the average was $60\pm9\%$.

Multiparametric analysis

**Combination of two parameters**

Compared with one parameter, the prevalence of a single combination of two parameters decreased from $35\pm9\%$ to $14\pm5\%$ (Figure 3).
Thirty-eight patients (21%) presented with two parameters only, 18 in the responders group (17%) and 20 in the non-responders group (26%). Patients with two parameters had a larger QRS width than others (150 ± 23 vs. 130 ± 20 ms, P = 0.015).

Eighty-five per cent of patients with a QRS width above 160 ms had at least two parameters.

The most frequently found combinations were EMD + ESD and LPED + IVD in 24% and 23% of patients, whereas AVD + RSDO or RSDO + EMD were rarely observed (6% and 5%).

Specificity for positive responder detection increased from 66 ± 12% to 88 ± 4% from one to two parameters. The increase in PPV was not so demonstrative (60 ± 9% to 62 ± 9%) and as expected sensitivity fell from 42 ± 14% to 17 ± 8%. Seventeen combinations were associated with a specificity less than 90%, eight combinations had a specificity higher than 90%, whereas only one surpassed 95% (RSDO + EMD). In terms of predictive positive value, four associations of two parameters reached the level of 70% (AVD + EMD, AVD + LPED, EMD + ESD, EMD + LPED), whereas IVD + RSDO generated the lowest value of PPV (<50%) (Table 3) (Figure 4).

**Combination of three and four parameters**

When combining three to four parameters, prevalence was 7 ± 4% and 3 ± 2% but specificities were 95 ± 3% and 98 ± 2%, respectively (Figure 4) (Table 2).

Ninety-six patients (53%) presented with three or more parameters, 60 in the responders group (68%) and 26 in the non-responders group (28%). Thirty per cent of these patients had a QRS width above 160 ms and 62% of patients with a QRS width above 160 ms had at least three parameters.

Only one combination of three parameters was associated with a specificity lower than 90% (IVD + SPWMD + LSDO) and one of four parameters with a specificity lower than 95% (IVD + EMD + ESD + LSDO). Positive predictive value was significantly higher.
than two to three and four parameters, respectively 61% to 65% and 70% ± 17% (Table 2). The highest PPVs for the combination of three criteria were observed for AVD + SPWMD + EMD and AVD + EMD + LPED, respectively 90% and 86%, whereas only the combination of four parameters reached the level beyond 90% of PPV.

Finally, significant relationships were observed between EF and ESV variations before and after CRT, and number of combined parameters (P = 0.02 for both, r = -0.26 and +0.27) (Figure 5) showing that higher the level of dyssynchrony the more demonstrative LV remodelling will be.

Global approach and reproducibility

Based on these results, we defined a global predictive score based on specificity and PPV. A low probability for having a good CRT response was forecast for patients with no parameter; a high probability for patients with at least three parameters or association of two parameters listed in Table 3; an intermediate probability for patients with one to two parameters (except parameters listed in Table 3). Intra- and inter-observer concordances generated Kappa at 0.89 and 0.82, respectively.

Discussion

Since the prevalence of heart failure is continuing to increase dramatically, improving the rate of response after CRT should be a major objective in order to improve the quality of life and survival of patients and to reduce unnecessary health expenditure. Previous small studies from one or two centres suggested that echocardiography could improve the selection of patients for CRT. This hypothesis has recently been questioned by the publication of the PROSPECT study.6 Based on demonstrating the lack of reproducibility of each parameter described in the literature, the authors concluded that no single echocardiographic measure of dyssynchrony may be recommended to improve patient selection for CRT beyond the current guidelines. Efforts aiming to reduce the variability arising from technical and interpretative factors may improve the predictive power of these echocardiographic parameters in a broad clinical setting.

However, from a global point of view, lack of reproducibility is an intrinsic part of the echocardiographic examination irrespective of the investigated target. LV function estimation, mitral regurgitation quantification, etc., are examples of the limitations of applying a single parameter in order to summarize the totality of abnormalities. Currently, almost 10 criteria are used in clinical routine to grade a mitral regurgitation. In contrast to CRT, independently of imaging modality, attempts have been made to reduce dyssynchrony to a single parametric approach. This has two consequences: first, it limits the detection of different expressions of dyssynchronies (AVD, IVD, intraventricular dyssynchronies, etc.). Contractility is an uncommon complex phenomenon in which chronologies are not superimposed irrespective of the deformation components.19,20 Second, in a more practical consideration, having a unique parameter in a specific patient can result in measuring erroneous values due to possible incompatibilities between the level of contractile abnormalities and the echocardiographic tool used for obtaining it.

We have taken a non-revolutionary but logical approach based on these two issues in an attempt, first, to reduce variability by non-forcing measurements of inappropriate parameters and allowing the use of other parameters and, second, to increase response rates by identifying and cumulating different levels of dyssynchronies. Penicka et al.16 first described the potential interest of associating IVD with an intraventricular dyssynchrony parameter showing improvement of specificity. More recently with a new echocardiography parameter such as TDI or strain, the combination of parameters seems to improve predictions of good responders.21
Based on a multicentre study that has included a significant number of patients \((n = 181)\), our main findings are: (i) a multiparametric approach for predicting CRT response makes it possible to limit the variability of parameters and (ii) the combination of two to four parameters increases the number of CRT responders by decreasing the number of false-positive cases.

Our feasibility rate was comparable to PROSPECT due to a homogeneous population from southwest Europe and the similar approaches taken by the three centres in investigating heart failure patients. In our study, the cut-offs for quantitative parameters were verified by ROC curves and concorded with those previously published. One major difference with PROSPECT and other studies was the ability to remove and not measure a specific parameter if it was identified as non-reliable in three consecutive beats. As a consequence, whereas SPWMD has a yield level of 72% and a variability of 72.1% in the PROSPECT study, its measurement was assessable in only 58% of our population but with a variability of 16%. Similar improvement in parameter reliability was observed for TDI parameters confirming that only reliable parameters in each individual case should be taken in account.

**Mechanical considerations**

It is thought that dysynchrony can be simplified to a QRS enlargement or a unique echocardiographic parameter. From MIRACLE to PROSPECT, there is proof that this ‘simple and naïve’ vision of dysynchrony does not result in an optimal selection of CRT patients. The necessity of a multiparametric approach lies in a more complex dysynchrony analysis. Example of simple acknowledgment can be observed in the integration of AVD. Because CRT devices include atrial detection/pacing capabilities as well as biventricular pacing, correction of AVD is one of the expected effects. In our population, AVD was observed in one-third of patients. Since AVD is well known to have hemodynamic consequence,22–24 to correct it may improve both functional status and LV function. Part of these effects cannot be underestimated in CRT patients as demonstrated in our study. Combining AVD with specific intraventricular dysynchrony parameters (EMD, LPED, or RSDO) makes it possible to identify good responders with greater accuracy than intraventricular parameters alone.

A more complex analysis stems from the recent description of timing or chronology in LV contraction separating several dimensions of deformations. On animal models, Sengupta et al.19 clearly demonstrated that aortic valve closure was not the marker of end-systolic contraction especially in the basal segments (re-orienting echocardiographic parameter to the mitral valve opening as suggested by Cazeau19), but also that longitudinal and circumferential strains do not line up during both systolic and diastolic phases. The hypothesis of dysynchrony expression in only one strain dimension and not all components has been raised by Bax et al.25 and was confirmed by our study with an average of just 31% of patients presenting a spatial dysynchrony in both the radial and longitudinal components. This is again a strong argument not to focus on one single parameter, irrespective of the applied tool, until a global and comprehensive tool could provide information on all contracting components (3D strain for example).

**Limitations**

- Our approach is limited by the number of centres, which could be increased on a larger and international scale. An interpretation bias exists due to the level of over-specialization of the three centres that are regional reference centres for heart failure patient investigations and CRT. This could overestimate the reproducibility of each parameter. However, our method is designed to limit the variability of measurements by allowing the operator to cancel measurements that he/she judges to be unreliable.

- Our analysis was mainly focused on specificity and false-positive values leaving sensitivity in a second place. It has to be clarified that our objective was not to remove EKG or other criteria10 from the CRT selection algorithm. From this guidelines based selection, our target was to increase responder patients by detecting future non-responders. By dramatically reducing false positive, this objective can be achieved.

- Definition of responder patients in our study is quite critical since it has been based only on LV remodelling and not on clinical status improvement which is the final CRT objective. However, placebo effect in CRT patients is a well-known phenomenon (≈40% of CRT-off patients in Miracle6) that limited the application of clinical status criteria in our study.

- In order to broaden this approach to all echocardiographic systems, we did not test the most recent tools such as 2D strain or real-time 3D which are highly dependent on the quality of windows. In a next step, these latest parameters should be included in a similar multiparametric approach in order to overcome their respective limitations.

- We are aware that our algorithm is not absolute. We used published parameters that respond partially to targeted end-points. For example, SPWMD analyses radial contraction between two opposite walls, whereas a comparison between all segments is necessary. Again, modern technology such as 2D strain may help to better identify LV dyssynchrony.

- Finally, global mechanical dysynchrony is the main target in the identification of CRT responders but should not overshadow other components of the response, such as LV mass, contractile reserve,26–27 the presence of extensive infarction scar,28 or dynamic dysynchrony.15 Lead position is also a significant determinant of CRT response especially in ischaemic cardiomyopathy.29

As a consequence, we preferred to limit the interpretation of our results in terms of CRT response probability and not in a binary way such as indication/contraindication.

**Clinical implications**

Our study demonstrated the absolute necessity to cumulate echocardiographic parameters for predicting good response to CRT. We identified specific combinations of two and more parameters associated with high specificity and positive predictive value for the identification of future CRT good responders. However, the simplification of our results is still required to produce a clinical impact. We propose to translate our combinations into a probability response scale (from low to high probability). The reproducibility of this judgement scale is compatible with a clinical
routine application. However, this algorithm needs to be evaluated in a large multicentre study even if a major step forward in using echocardiographic parameters has been demonstrated and clarified in this study by applying this multiparametric approach.

Conflict of interest: None declared.

References


