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Clinical research

Clinical and electrocardiographic predictors of a positive response to cardiac resynchronization therapy in advanced heart failure

Guillaume Lecoq[1], Christophe Leclercq[1], Emmanuelle Leray[2], Christophe Crocq[1], Christine Alonso[1], Christian de Place[1], Philippe Mabo[1], and Claude Daubert[1]*

[1] *Department of Cardiology, Centre Hospitalier Universitaire, Rennes F-35000, France*
[2] *Department of Public Health, Centre Hospitalier Universitaire, Rennes F-35000, France*

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KEYWORDS
Cardiac resynchronization therapy;
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Aims Cardiac resynchronization therapy (CRT) is an effective treatment for refractory congestive heart failure (CHF). However, up to 30% of patients do not respond to CRT. The aim of this study was to identify clinical and electrocardiographic (ECG) predictors of a positive response to CRT.

Methods and results This retrospective study included 139 consecutive patients successfully implanted with a CRT device (mean age, 68 ± 9 years, 113 men). At baseline, 69% of patients were in New York Heart Association (NYHA) functional class III, and 31% in class IV, mean left ventricular ejection fraction was 21 ± 6%, and mean QRS duration was 188 ± 28 ms. In each patient, left and right ventricular leads were placed to attain the shortest QRS duration during biventricular stimulation. Patients were classified at 6 months as responders to CRT ($n = 100$) if they were alive, they had not been re-hospitalized for management of CHF, and the NYHA class had decreased by 1 point, and/or peak VO_2 or 6 min hall-walk increased by >10%. All others were classified as non-responders ($n = 38$; one patient was lost to follow-up). Uni- and multivariate logistic regression analyses were performed to detect a pre- or intra-operative predictor of a positive response to CRT. Among multiple demographic, clinical, and ECG variables, the amount of QRS shortening (ΔQRS) associated with biventricular stimulation was the only independent predictor of a positive (37 ± 23 ms) vs. negative (11 ± 23 ms) response to CRT ($P < 0.001$).

Conclusion A positive response to CRT was observed in 73% of patients at 6 months and predicted only by ΔQRS.

Introduction

The effectiveness of cardiac resynchronization therapy (CRT) in patients with advanced congestive heart failure (CHF) refractory to medical treatment has been amply confirmed.[1] CRT is now indicated for patients in sinus rhythm and New York Heart Association (NYHA) functional class III or IV, with left ventricular (LV) systolic dysfunction, LV end-diastolic diameter (EDd) >55 mm, LV ejection fraction (EF) <35%, and a QRS duration >130 ms on standard surface electrocardiogram (ECG).

* Corresponding author. Tel: +33 2 99 28 25 25; fax: +33 2 99 28 25 10;
E-mail address: jean-claude.daubert@chu-rennes.fr

Randomized studies have demonstrated a benefit conferred by CRT on symptoms of CHF and exercise capacity.[2–7] Although this treatment is effective in the majority of patients, up to 30% of patients are considered 'non-responders'. Identifying reliable predictors of effectiveness of CRT remains a major challenge in clinical practice, particularly from the perspective of patient selection. Few studies have examined the intra-operative criteria of mid- to long-term effectiveness of this therapy. We performed this analysis to identify simple baseline predictive factors of a positive response to CRT.

Methods

Inclusion criteria

All patients who underwent successful implantations of biventricular stimulation systems between August 1994 and July 2001 were retrospectively included in this analysis. Criteria for implantation of a CRT system included: (i) CHF and NYHA functional class III or IV refractory to optimal medical management as defined by current guidelines,[6] (ii) LVEF $<35\%$ and LVEDd >60 mm measured echocardiographically, and (iii) intraventricular conduction defects, manifest as a surface ECG QRS duration >150 ms in patients with spontaneous ventricular activation, or ≥ 200 ms in patients previously paced in the right ventricle.

Implantation techniques

An endovenous LV lead was implanted in a coronary sinus tributary in all cases,[7] with a view to achieve permanent epicardial stimulation from a lateral or posterolateral vein or, when it was unattainable, from the mid- or great cardiac vein. The right ventricular (RV) lead was then implanted whether at the RVOT, the septum, the anterior wall, or the apex, according to the result of intra-operative biventricular pace mapping looking at the shortest biventricular paced QRS duration. Final lead positioning was assessed from post-operative chest X-ray in anterio-posterior and lateral view.

Patients in sinus rhythm received an atrio-biventricular pulse generator programmed in DDD(R) mode and interfaced with a bipolar right atrial and both ventricular leads. The atrio-biventricular delay was optimized individually on the basis of Doppler echocardiographic measurements of transmitral flow.[8] Patients in permanent atrial fibrillation received a dual chamber pulse generator programmed in DDD(R) mode, with the LV lead interfaced with the atrial channel and the RV lead with the ventricular channel. The AV, i.e. interventricular delay was programmed at a minimal interval of 30 ms to achieve the greatest degree of biventricular fusion. Radiofrequency atrioventricular junctional ablation was performed at the time of CRT system implantation to guarantee complete and permanent biventricular capture.

Collection of outcome measures

From a review of medical records, the following variables were recorded at baseline and up to 6 months after CRT system implantation: (i) NYHA functional class, (ii) exercise capacity from the distance covered during a 6 min hall-walk and peak exercise O_2 consumption (peak VO_2), (iii) QRS duration and axis, (iv) echocardiography measurements of LVEF and LEDd, (v) hospitalizations for decompensated CHF, (vi) vital status.

Study groups assignment

The study population was divided in two groups on the basis of the assessment of the clinical composite response, as currently applied by heart failure specialists.[9] A positive response to CRT at 6 months included: (i) alive status, (ii) no interim hospitalization for decompensate CHF, and (iii) a ≥ 1 point decrease in NYHA functional class or, if NYHA was unchanged, a $>10\%$ increase in peak VO_2, in the distance covered during a 6 min walk, or in both.

Statistical analyses

Unless otherwise specified, results are presented as mean $\pm$ standard deviation (SD). Efficacy of CRT was examined by comparing variables at baseline vs. 6 months after implantation of the biventricular pacing system. Differences between baseline and 6 months were tested by the Student's *t*-test for paired samples for comparisons of quantitative variables and by the Mc Nemar test for comparisons of qualitative variables. A univariate, logistic regression analysis was used for identifying pre- and intra-operative variables to be predictive of a positive response to CRT, including age, underlying heart disease, absence vs. presence of prior permanent ventricular pacing, sinus rhythm vs. atrial fibrillation, QRS duration before and during biventricular stimulation and the difference between the two values (ΔQRS), NYHA class, LVEF, LVEDd, and RV and LV lead position. Only variables significant at the 0.25 level in the univariate analysis were included in the multivariable logistic regression. Then variables were selected according to a step-down stepwise procedure using likelihood ratio statistic (then interactions between these variables will be explored, if there are at least two variables in the final model). Finally, the goodness-of-fit was assessed with the Hosmer and Lemeshow's test. $P < 0.05$ was considered statistically significant and all tests were two-sided. No correction of type 1 error for multiple tests was performed.

Results

Study population

During the study period, transvenous biventricular pacemaker implantation was attempted in 158 patients and successfully performed in 88% patients that constitute the study population. The implantation success rate increased progressively from the very preliminary experience (61% in 1994–96) to the latest (98% in 2000–01). Detailed technical data have already been reported.[10]

The study population included 139 patients (mean age, 68 ± 9 years; 113 men). A non-ischaemic dilated cardiomyopathy was present in 54%, ischaemic heart disease in 35%, and miscellaneous disorders in 11% of patients (*Table 1*). At the time of CRT system implantation, 96 patients were in NYHA functional class III and 43 in class IV. Sinus rhythm was present in two-thirds and permanent atrial fibrillation in one-third of patients. A dual chamber permanent pacemaker had been previously implanted for conventional anti-bradycardia indications in 23 and a VVI pacemaker in 13 patients. QRS duration ranged from 150 to 260 ms (mean, 188 ± 28 ms) and

Table 1 Baseline characteristics of the overall study population ($n = 139$)

Men/women (*n*)	113/26
Age (years)	68 ± 9
Heart failure aetiology (*n*)	
Idiopathic dilated cardiomyopathy	75
Ischaemic cardiomyopathy	49
Others	15
Prior cardiac pacing (% of patients)	26
Duration of symptoms (years)	7 ± 5
Sinus rhythm/atrial fibrillation (*n*)	94/45
PR interval (ms)	239 ± 55
LBBB/RBBB/non-specific IVCD (*n*)	127/6/6
QRS duration (ms)	188 ± 28
Frontal QRS axis (°)	−31 ± 49
LVEF (%)	21 ± 6
LVEDd (mm)	71 ± 8
NYHA functional class III/IV (*n*)	96/43
Distance walked in 6 min (m)	309 ± 105
Peak VO_2 (mL/kg/min)	13.4 ± 3.4

Unless specified otherwise, values are mean ± SD. LBBB, left bundle branch block; RBBB, right bundle branch block; IVCD, intraventricular conduction defect.

was significantly longer in previously paced (210 ± 25 ms) than non-paced (181 ± 25 ms) patients ($P < 0.001$). The LV lead was implanted in a lateral or a posterolateral vein in 73% of cases. The RV lead was positioned at the septum or the anterior wall in 72%. This relative proportion of apical and non-apical RV leads was not significantly different in previously paced patients (33 vs. 63%) when compared with patients with intrinsic conduction (23 vs. 77%).

Six month outcomes

During the 6 month period of observation, four patients died of endstage CHF, one died suddenly, and one patient died of a non-cardiac cause. Among the survivors ($n = 133$), the repartition of the NYHA functional class was very different, as shown in *Figure 1* ($P < 0.001$), whereas peak VO_2 increased from 13.4 ± 3.5 to 16.1 ± 4.0 mL/kg/min ($P < 0.001$), distance covered in 6 min from 309 ± 105 to 370 ± 103 m ($P < 0.001$), and LVEF from 20 ± 6 to 27 ± 9% ($P < 0.001$). Biventricular stimulation shortened the mean QRS duration from 188 ± 28 to 159 ± 21 ms ($P < 0.001$), and shifted the frontal QRS axis from −32 ± 49 to +58 ± 69° ($P < 0.001$, *Table 2*).

Characteristics of responders vs. non-responders to CRT

A positive response was observed in 100 patients (72%), whereas 38 patients (27%) were not clinically improved by CRT. One patient was lost to follow-up. The baseline characteristics of the two groups were generally similar, including functional capacity and echocardiographic measurements (*Table 3*), as well as the sites of implantation of the LV and RV leads (*Table 4*). Comparisons of 6 months clinical characteristics between the two groups are shown in *Table 5*. Among all variables examined, the

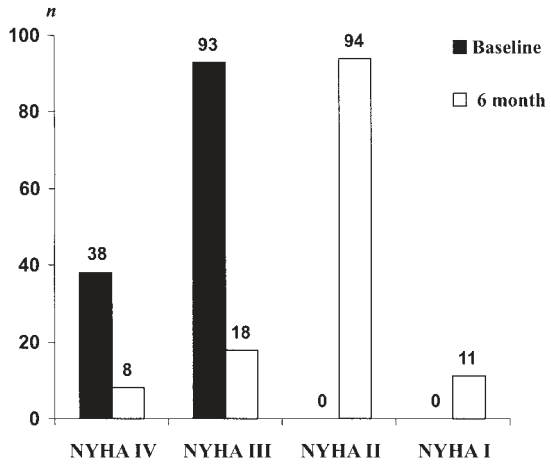

Figure 1 Distribution of NYHA functional classes at baseline and after 6 months of CRT.

only significant differences detected were derived from the surface ECG. In univariate analysis, QRS duration before CRT was longer in responders (192 ± 27 ms) than in non-responders (180 ± 29 ms, $P < 0.001$), whereas it was shorter in responders (155 ± 20 ms) than in non-responders (169 ± 20 ms) during CRT ($P < 0.001$). Among responders, QRS duration during CRT decreased in 95%, increased in 2%, and remained unchanged in 3%. Among non-responders, QRS decreased in 60%, increased in 27%, and remained unchanged in 13%. Finally, the mean QRS shortening (ΔQRS) associated with CRT when compared with baseline was significantly greater among the responders (37 ± 23 ms) than the non-responders (11 ± 23 ms, $P < 0.001$, *Table 4* and *Figure 2*). However, no clear-cut value could be found for separating responders and non-responders. This result was principally observed in patients with baseline intrinsic conduction (*Table 6*). A similar trend was also observed in the subgroup of previously paced patients, but did not reach statistical significance threshold probably owing to the small number of patients. No significant differences were observed between patients with normal sinus rhythm and patients with permanent AF even though an additional 30 ms interventricular delay was mandatory applied in AF patients.

A receiver operating characteristic curve analysis failed to identify a cut-off value of ΔQRS. ΔQRS was thus considered as a continuous variable and included in the logistic regression with a 20 ms step.

The univariate logistic regression showed that QRS duration during CRT and ΔQRS was significantly associated with response ($P < 0.018$ and $P < 0.001$).

The multivariable logistic regression showed that ΔQRS emerged as the only independent predictor of response to CRT (for a step of 20 ms: odds ratio 2.15, 95% confidence interval 1.46–3.17, $P < 0.001$)

Discussion

Since the first report, in 1994, of the implantation of a biventricular cardiac stimulator to improve the

Table 2 Baseline and 6 month clinical data in the overall study population (paired observations)

	n	Baseline	6 months	*P*-value
NYHA functional class				
Class I/II/III/IV (*n*)	131	0/0/93/38	11/94/18/8	<0.001
Distance walked in 6 min (m)	75	312 ± 105	370 ± 103	<0.001
Peak VO_2 (mL/kg/min)	82	13.4 ± 3.5	16.1 ± 4.0	<0.001
LVEF (%)	115	20 ± 6	27 ± 9	<0.001
QRS duration (ms)	131	189 ± 28	159 ± 21	<0.001
Frontal QRS axis (°)	131	−32 ± 49	58 ± 69	<0.001

Unless specified otherwise, values are mean ± SD.

Table 3 Comparisons of baseline demographic, clinical, and functional characteristics in responders vs. non-responders to CRT

	Responders ($n = 100$)	Non-responders ($n = 38$)	*P*-value
Age (years)	68 ± 9	69 ± 9	0.7
Men/women (*n*)	79/21	33/5	0.8
Heart failure aetiology (*n*)			
Ischaemic cardiomyopathy	35	13	1
Non-ischaemic cardiomyopathy	65	25	
Duration of symptoms (years)	7 ± 5	8 ± 5	0.2
Prior cardiac pacing (% of patients)	27	24	0.2
NYHA functional class I/II/III/IV	0/0/72/28	0/0/24/14	0.3
Distance walked in 6 min walk (m)	318 ± 102 (n = 75)	274 ± 109 (n = 21)	0.09
Peak VO_2 (mL/kg/min)	13.4 ± 3.6 ($n = 76$)	13.6 ± 3.1 ($n = 27$)	0.8
LVEF (%)	21 ± 6	19 ± 6	0.053
LVEDd (mm)	71 ± 9	73 ± 8	0.2
Mitral insufficiency, grade 1/2/3 (*n*)	18/35/28	2/16/12	0.3

Unless specified otherwise, values are mean ± SD.

haemodynamic status,[11] this adjunctive treatment of refractory CHF has markedly evolved. Several studies have demonstrated the feasibility,[12] safety,[13] and efficacy of this new form of management of advanced CHF.[2–4] The present analysis confirms the mid-term benefits conferred by biventricular stimulation in our own population. The improvement was not limited to symptoms, measured by the NYHA functional classification, but extended to exercise capacity, tested by the distance covered in a 6 min hall-walk and by measurement of peak VO_2. Our results are similar to other reports with respect to the 6 min walk and the VO_2 peak, including controlled studies like MUSTIC and MIRACLE trials.[2,4] On the other hand, the nearly 30% rate of non-responders in our study matched with those observed in other studies.[14,15]

In our comparison of responders vs. non-responders, the only predictor of a therapeutic benefit conferred by biventricular stimulation was the magnitude by which it decreased the QRS duration. Although, in this study, this observation was highly predictive, other studies reached different conclusions.[14–16] They differed, however, from ours in two main respects. First, the criteria used by others to define responders have been variable and often limited to changes in NYHA functional class,[14,15] whereas we applied a robust composite endpoint, combining a subjectively derived measurement (NYHA class) with objective outcomes, including mortality and heart failure hospitalization. We believe, as recommended by Packer,[9] that this represents a more global assessment of the patient. Secondly, in the present study, the RV implantation site was selected on a patient-to-patient basis, to obtain the shortest QRS duration during biventricular stimulation, whereas, in other studies, the RV lead was generally implanted at the apex.[14–17]

On the basis of the known pathophysiology of electromechanical disorders, the change in QRS duration produced by biventricular stimulation should represent the quality of electrical resynchronization and indirectly reflect the degree of correction of electromechanical abnormalities. Though their observation remains controversial, Kim *et al.*[18] reported that the decrease in QRS duration was correlated with an increase in systolic ejection volume, via a decrease in LV end-diastolic volume. This has a direct intra-operative impact on the choices of LV and RV ventricular pacing sites, which should aim at attaining the narrowest QRS possible. Although there is general agreement regarding the lateral position of the LV lead, there is no consensus for the placement of the RV lead. Pending the validation of this recommendation by dedicated prospective studies, it appears important, for the time being, to implant the RV lead at a site associated with the shortest QRS duration during biventricular pacing.

In the multivariable analysis, we found no reliable preoperative predictor of a positive response to CRT,

Table 4 Comparisons of baseline electrocardiographic data in responders vs. non-responders to CRT

	Responders ($n = 100$)	Non-responders ($n = 38$)	*P*-value
Sinus rhythm/atrial fibrillation (*n*)	69/31	24/13	0.2
LBBB or non-specific IVCD/RBBB	94/4	35/2	0.7
PR interval (ms)	236 ± 49	254 ± 71	0.6
QRS duration (ms)			
Pre-implantation of CRT system	192 ± 27	180 ± 29	0.018
Post-implantation of CRT system	155 ± 20	168 ± 20	<0.001
ΔQRS (ms)	37 ± 23	11 ± 27	<0.001
Frontal QRS axis (°)			
Pre-implantation of CRT system	−36 ± 40	−25 ± 63	0.3
Post-implantation of CRT system	55 ± 64	70 ± 79	0.3
LV lead position (% of patients)			
Lateral	74	73	0.9
Other	26	27	
RV lead position (% of patients)			
Septum or anterior	74	69	0.6
apex	26	31	

Unless specified otherwise, values are mean ± SD. LBBB, left bundle branch block; RBBB, right bundle branch block; IVCD, intraventricular conduction defect. ΔQRS = QRS duration before −QRS duration after CRT implantation.

Table 5 Comparisons of the 6 month clinical outcomes in responders vs. non-responders to CRT

	Responders ($n = 100$)	Non-responders ($n = 38$)	*P*-value
NYHA functional classes			
IV	0	8	
III	4	12	<0.001
II	85	11	
I	11	0	
Distance covered in 6 min walk (m)	395 ± 86	269 ± 108	<0.001
Peak VO_2 (mL/kg/min)	16.8 ± 4	14 ± 3.7	0.003
Death	0	5	

Unless specified otherwise, values are mean ± SD.

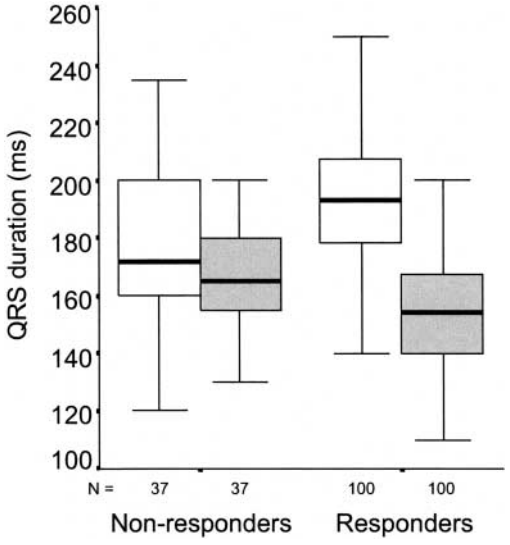

Figure 2 Baseline and paced QRS duration in responders and non-responders: White boxes, pre-op; grey boxes, post-op.

including the baseline QRS complex duration even if there was a significant trend in univariate analysis. Aurrichio *et al.* (19) and Kass *et al.* (20) found a QRS duration >150 ms to be predictive of a haemodynamic improvement in the acute setting. In contrast, our observations suggest that, in a population of patients with a markedly prolonged QRS at baseline (a mean of nearly 190 ms in this study), a 10 or 20 ms decrease is not as reliable in its prediction of a favourable electromechanical response as in the presence of a QRS < 150 ms. Among other pre-operative variables, the quantification of intra- and interventricular asynchrony by new echocardiographic imaging methods appears promising. Using Doppler echocardiographic techniques, Yu *et al.*[21] identified the homogenization of regional ventricular contraction to be the main mechanism behind effective cardiac resynchronization, and Pitzalis *et al.*[16] found responders to CRT to have a significantly longer septal-to-posterior wall motion delay at baseline than the non-responders. Furthermore, Soogard *et al.*[22] found a correlation between increase in LVEF and severity of baseline ventricular desynchronization on tissue Doppler imaging. However, in the latter two studies, the criterion defining the response to CRT was limited to changes in LVEF and did not include long-term clinical outcomes. In another tissue Doppler echocardiographic study, Ansalone *et al.*[23] observed that the greatest clinical improvement among patients in whom the LV was stimulated in the myocardial region activated last during spontaneous rhythm. This study highlighted the importance of individualizing the choice of LV stimulation site, and also illustrated the challenge represented by such pursuit, as it was effectively achieved in just over 40% of patients. Although these various techniques of ventricular regional analysis may become an indispensable adjunct to the surface ECG,

Table 6 Changes in QRS duration in patients with or without previously implanted pacemaker

	Patients without previous pacemaker ($n = 101$)			Patients with previous pacemaker ($n = 37$)		
	Responders ($n = 72$)	Non-responders ($n = 29$)	*P*-value	Responders ($n = 28$)	Non-responders ($n = 9$)	*P*-value
QRS duration (ms)						
Pre-implantation	185 ± 25	170 ± 22	<0.01	212 ± 23	211 ± 28	0.91
Post-implantation	152 ± 20	162 ± 15	0.01	164 ± 18	187 ± 22	<0.01
ΔQRS (ms)	33 ± 23	8 ± 45	<0.001	47 ± 21	23 ± 36	0.09

they remain to be validated in larger patient populations over longer periods of observation. The ongoing CARE-HF trial,[24] which uses echocardiographic dyssynchrony as one of its criteria for the selection of candidates for CRT, should provide information in this regard.

Study limitations

As our study was retrospective, some data were not available in all patients. So this study is based on an intra-patient comparison.

Patient heterogeneity (stable sinus rhythm vs. permanent AF; intrinsic conduction vs. paced rate) may have influenced the results. Furthermore, our population included patients treated as long as 10 years ago, much before publication of echocardiographic evaluations of mechanical dyssynchrony, limiting our collection of truly comparable data. However, despite the growing emphasis put on several echocardiographic criteria of cardiac dyssynchronization, they all remain to be prospectively validated in randomized studies.

Conclusions

This analysis provides further confirmation of the intermediate-term benefits conferred by CRT which, based on a set of robust clinical criteria, was effective in >70% of our patients. No pre-operative clinical or ECG characteristic allowed the distinction of responders vs. non-responders to CRT, and the only reliable predictive criterion was the degree of QRS shortening associated with biventricular stimulation. This observation has practical implications, particularly with regard to the choice of LV and RV stimulation sites. It is likely that, combined with a refined pre-operative patient selection based on echocardiographic electromechanical imaging, the pursuit of this simple ECG criterion will decrease the proportion of non-responders to CRT and increase the overall clinical efficacy of this highly promising treatment.

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