Predictive parameters of left ventricular reverse remodeling in response to cardiac resynchronization therapy in patients with severe congestive heart failure

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Cardiac resynchronization therapy; Heart failure.

Background. **Cardiac resynchronization therapy (CRT) is useful for the treatment of severe congestive heart failure. Unfortunately up to 30% of patients could be non-responders. The aim of our study was to find parameters to predict responsiveness to CRT.**

Methods. **Fifteen patients (9 males, 6 females, mean age 67.3 ± 7.8 years, range 52-83 years) with dilated cardiomyopathy, NYHA functional class III-IV, left ventricular (LV) ejection fraction < 35% and QRS ≥ 110 ms, underwent CRT. All the patients had echocardiographic evidence of systolic dyssynchrony.**

Results. **One patient died of electromechanical dissociation. The remaining 14 patients maintained biventricular stimulation at 6 months; mean QRS width decreased from 156 to 132 ms (p < 0.001). Ten patients (71%) were considered responders because of a reduction in LV end-systolic volume > 15%. In non-responders (4 patients, 29%) LV end-systolic volume was stable in 3 patients and increased in 1. LV ejection fraction significantly increased only in responders (p < 0.001). Responders had more severe pre-pacing dyssynchrony than non-responders (p < 0.001). Inter- (p = 0.002) and intraventricular dyssynchrony (p = 0.003) did significantly reduce after CRT only in responders. On multiple regression analysis there were two independent predictors of reverse remodeling after pacing: the baseline mitral QS-tricuspid QS (QSm-QSt) time (ß = -1.7, p = 0.005) and the intraventricular dyssynchrony index (ß = -1.55, p = 0.007). Pre-implant QSm-QSt of 38 ms correctly identified the two groups: responders had a value > 38 ms and non-responders < 38 ms. The pre-implant intraventricular dyssynchrony index of 28 ms was the cut-off value: responders had an index > 28 ms, non-responders < 28 ms.**

Conclusions. **In the literature a tissue Doppler imaging index of intraventricular dyssynchrony evaluated before implantation is used to select responders to CRT. In our work we studied interventricular and intraventricular dyssynchrony, and both the QSm-QSt time and the standard deviation of the 12 LV segment QS time were correctly able to identify responders.**

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Introduction

Cardiac resynchronization therapy (CRT) improves acute hemodynamic parameters[1,2], NYHA class, quality of life, exercise capacity, peak oxygen uptake[3] and probably reduces mortality[4] in heart failure patients with widened QRS. Biventricular pacing results in left ventricular (LV) reverse remodeling: a reduction in volumes and diameters, an increase in ejection fraction and a reduction in mitral regurgitation[5]. Anyway, there are patients (up to 30%) who do not respond to CRT[1,4].

The aims of our work were: a) to examine differences in benefits on clinical endpoints, cardiac function and synchronicity between responders and non-responders of LV reverse remodeling; b) to find out predictors of successful reverse remodeling that might help to select patients who will respond to CRT.

Methods

Patients. Fifteen patients (9 males, 6 females, mean age 67.3 ± 7.8 years, range 52-83 years) with dilated cardiomyopathy and congestive heart failure (CHF), NYHA functional class III (n = 10) and IV (n = 5), LV ejection fraction < 35% (none with restrictive diastolic pattern) and basal QRS duration ≥ 110 ms, underwent biventricular pacing therapy. Nine patients (60%) were on sinus rhythm and 6 (40%)

had chronic atrial fibrillation. A complete left bundle branch block was present in 10 patients (67%); 4 subjects (26%) had intraventricular conduction delay and 1 (7%) had QRS duration of 110 ms. The PR interval was > 200 ms in 4 subjects (44% of those on sinus rhythm). Etiology of CHF was ischemic in 8 (6 males, 53%) and non-ischemic in 7 patients (3 males, 47%). Six patients (40%, 5 with ischemic CHF) received CRT plus cardioverter-defibrillator (ICD) implantation. Medications included diuretics in all patients; ACE-inhibitors in 12, angiotensin receptor antagonists in 3, beta-blockers (carvedilol) in 11, spironolactone in 10, and digoxin in 8 patients. All patients were symptomatic, but hemodynamically stable, and were receiving maximal tolerated doses of drugs for at least 1 month before enrollment.

Study protocol. The evaluation of patients was performed before (baseline) and 6 months after implantation. Patients underwent: clinical evaluation and ECG, Minnesota Living with Heart Failure Questionnaire for quality of life assessment, echocardiography, 6-min walk test, and cardiopulmonary exercise treadmill test. The study complies with current ethical considerations and all patients gave their written informed consent.

Device implantation. All the patients receiving CRT had echocardiographic evidence of ventricular systolic dyssynchrony. The system for LV pacing lead implantation was Easytrak over-the-wire (Guidant, model 4517) in all patients except one (Medtronic Attain System, model 2187). The biventricular device was Contak TR CHFD model 1241 (Guidant) or InSync (Medtronic). The location of the LV pacing lead was: lateral vein in 6 cases, postero-lateral in 3, posterior in 3, anterior in 2, and anterolateral in 1. Biventricular pacemakers were successfully implanted in all patients without complications between March 2002 and September 2003. After implantation the atrioventricular interval was optimized for maximal diastolic filling using Doppler echocardiography.

Echocardiography. Standard echocardiography was performed in all patients at baseline and at 6-month follow-up (ATL system). LV volumes and ejection fraction were assessed by Simpson's equation using the apical 2- and 4-chamber views. Patients were considered responders of reverse remodeling if the LV end-systolic volume was reduced > 15% compared with baseline values, and non-responders if it was reduced < 15%: thus, for our study we considered "volumetric responders" as already reported by Yu et al.[6] and Auricchio et al.[7]. LV diastolic function was evaluated by pulsed wave Doppler echocardiography (transmitral flow velocity curve) and by pulsed wave tissue Doppler imaging (PW-TDI). The presence and severity of mitral regurgitation was assessed by the percent jet area relative to the left atrial size in the apical 4-chamber view.

For the evaluation of systolic synchronicity we used continuos wave TDI and PW-TDI at apical 4-chamber, 2-chamber and long-axis views for the major axis motion of the ventricles. After adjustments of filter frequency, gain settings, pulse repetition frequency and color saturation, at least three consecutive beats were stored and the images were digitized and analyzed offline. The interventricular delay was assessed by continuous wave Doppler as the difference between "Q wave-aortic flow onset" interval and "Q wave-pulmonary flow onset" interval. A difference ≥ 40 ms indicated a significant interventricular delay. By PW-TDI we evaluated the difference between "Q wave-systolic S wave onset" interval on the lateral mitral hemiannulus (mitral QS time [QSm]) and "Q wave-S wave onset" interval on the lateral tricuspid annulus (tricuspid QS time [QSt]). The difference QSm-QSt indicated interventricular delay if positive[6,8,9]. The intraventricular delay was evaluated by PW-TDI calculating the QS times of 12 LV segments (anteroseptal, posteroseptal, anterolateral, posterolateral, inferior and anterior; basal and mid-segmental). The standard deviation (SD) of the 12 LV segment QS times was calculated in each patient as index of intraventricular systolic dyssynchrony.

The evaluation of inter- and intraventricular systolic synchronicity was also performed in 15 normal control subjects (6 males, 9 females, mean age 65 ± 5 years, range 55-70 years). They had no history of cardiovascular or systemic disease and had normal physical, ECG and echocardiographic examinations.

Statistical analysis. All data are expressed as mean ± SD; a p value < 0.05 was considered as statistically significant. To examine the predictors of reverse remodeling in a univariate model, correlation analysis was used for parametric variables and Pearson χ^2 test for non-parametric variables. The multivariate regression analysis was performed using the changes in LV end-systolic volume as dependent covariates.

Results

All implantations were successful and without complications. No patient was pacing-dependent. During 6-month follow-up, 1 patient died of electromechanical dissociation caused by severe hyperkalemia in end-stage renal failure. The remaining 14 patients maintained biventricular stimulation at 6-month follow-up; mean QRS duration decreased from 156 ± 21 to 132 ± 16 ms (p < 0.001).

Responders and non-responders. Ten patients (71%) were responders with a reduction in LV end-systolic volume > 15% compared to baseline (mean reduction -31.2 ± 5.5%). In non-responders (4 patients, 29%) LV end-systolic volume was stable in 3 patients and further increased in 1 (mean variation +1.4 ± 1.1% compared to baseline). The mean variation in LV end-diastolic volume was -22.4 ± 10.1% in responders and +1.8 ± 0.9% in non-responders. Table I shows the differences regarding baseline variables between responders and non-responders; table II shows the variations of all studied parameters at 4-month follow-up.

Clinical evaluation. NYHA functional class was improved in all responders (100%) but only in 1 out of 4 non-responders (25%) ($\chi^2 = 9.4$, $p = 0.003$). Peak oxygen uptake ($p = 0.002$), the metabolic equivalent achieved during exercise test ($p = 0.003$), and 6-min walk test ($p = 0.007$) increased only in responders. The quality of life score improved in both groups (Table I).

Systolic and diastolic function and synchronicity indexes. LV ejection fraction significantly increased only in responders compared to baseline ($p < 0.001$); in non-responders it was unchanged. Mitral regurgitation area significantly decreased only in responders (p

Table I. Comparison of baseline parameters between responders and non-responders.

Baseline parameters	Non-responders (n=4)	Responders (n=10)	p
Age (years)	69.7 ± 4.6	66.6 ± 9.1	NS
Sex (M/F)	3/1	5/5	
Etiology	2 ischemic/ 2 non-ischemic	5 ischemic/ 5 non-ischemic	NS
LBBB	1 (25%)	8 (80%)	< 0.05
NYHA class	3.25	3.4	NS
QRS (ms)	149 ± 15	168 ± 30	< 0.05
6MWT (m)	335 ± 151	312 ± 32	NS
Quality of life	40.9 ± 30.6	35.6 ± 24.7	NS
METS	3.8 ± 1.2	4.1 ± 1.1	NS
VO_2 peak (ml/kg/min)	14.7 ± 3.8	13.7 ± 2.9	NS
LVEDV (ml)	155.2 ± 40.9	197.3 ± 44.7	< 0.05
LVESV (ml)	114.7 ± 38.6	155.4 ± 19.9	< 0.05
Ejection fraction (%)	29.2 ± 7.4	27.6 ± 4.7	NS
Mitral regurgitation (% LA area)	36 ± 20	30 ± 12	NS
Diastolic filling time (ms)	345 ± 101	354 ± 17	NS
QSm-QSt (ms)	28.4 ± 7.8	48.6 ± 10.8	< 0.05
Intra-v-d index (ms)	17.5 ± 4.2	37.9 ± 6	< 0.05

6MWT = 6-min walk test; Intra-v-d = intraventricular delay; LA = left atrial; LBBB = left bundle branch block; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; METS = metabolic equivalents; QSm = interval between Q wave and tissue Doppler S wave on the mitral annulus; QSt = interval between Q wave and tissue Doppler S wave on the tricuspid annulus.

Table II. Comparison of all studied parameters at 4-month follow-up after cardiac resynchronization therapy in responders vs non-responders to left ventricular reverse remodeling.

Parameters	Non-responders (n=4)		Responders (n=10)	
	4 months	p*	4 months	p*
NYHA class	3	0.06	2	0.003
QRS (ms)	132 ± 16	0.01	139 ± 18	0.005
6MWT (m)	371 ± 22	NS	397 ± 28	0.007
Quality of life	22.7 ± 18.7	0.03	19.2 ± 15.7	< 0.001
METS	3.6 ± 0.7	NS	6.2 ± 1.4	0.003
VO_2 peak (ml/kg/min)	13.9 ± 1.6	NS	19.3 ± 4.7	0.002
LVEDV (ml)	156.5 ± 12.6	NS	139.4 ± 28.1	< 0.001
LVESV (ml)	116.3 ± 41.1	NS	85.6 ± 12.2	< 0.001
Ejection fraction (%)	30.4 ± 6.6	NS	38.7 ± 11.6	< 0.001
Mitral regurgitation (% LA area)	29 ± 12	NS	14 ± 7	< 0.001
Diastolic filling time (ms)	366 ± 99	NS	478 ± 15	< 0.001
QSm-QSt (ms)	30.3 ± 6.7	NS	28.7 ± 7.7	0.002
Intra-v-d index (ms)	17.9 ± 6.5	NS	21.2 ± 9.5	0.003

6MWT = 6-min walk test; Intra-v-d = intraventricular delay; LA = left atrial; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; METS = metabolic equivalents; QSm = interval between Q wave and tissue Doppler S wave on the mitral annulus; QSt = interval between Q wave and tissue Doppler S wave on the tricuspid annulus. * vs baseline.

< 0.001). LV diastolic filling time increased only in responders ($p < 0.001$). Responders to reverse remodeling had more severe systolic dyssynchrony before pacing than non-responders, in terms of both inter- and intraventricular delay ($p < 0.001$). QSm-QSt interval (interventricular delay) was significantly reduced in responders after biventricular pacing ($p = 0.002$), while it was increased in non-responders. Also the intraventricular dyssynchrony index (intraventricular delay) was significantly reduced only in responders after pacing ($p = 0.003$) (Table I).

Arrhythmic events. At follow-up we did not find any life-threatening ventricular arrhythmia (sustained ventricular tachycardia, ventricular fibrillation) in both the CRT and CRT+ICD group. The patient who died after 3 months received CRT+ICD and the event that caused death was electromechanical dissociation caused by severe hyperkalemia in end-stage renal failure.

Predictors of left ventricular reverse remodeling. On a univariate model there was no difference in age, gender, etiology of CHF, baseline NYHA functional class, baseline QRS duration, and baseline PR interval between responders and non-responders. We found a trend toward a greater number of patients with left bundle branch block in responders than in non-responders ($\chi^2 = 3.3$, $p = 0.07$). The same non-significant trend was found for the degree of shortening of QRS after pacing ($\chi^2 = 2.9$, $p = 0.09$). None of the remaining pre-implant clinical parameters (6-min walk test, quality of life, maximal metabolic equivalent, peak oxygen uptake) was able to predict responsiveness to CRT. For echocardiographic parameters the most significant predictor of reverse remodeling was the severity of systolic dyssynchrony before pacing. In particular, both a large baseline QSm-QSt interval and a large baseline intraventricular dyssynchrony index were correlated with a greater reduction in LV end-systolic volume at 6 months ($r = -0.84$, $p < 0.001$ for interventricular delay; $r = -0.78$, $p < 0.001$ for intraventricular delay). For the other echocardiographic parameters we did not find any correlation.

On multiple regression analysis there were two independent predictors of reverse remodeling after biventricular pacing: baseline QSm-QSt ($ß = -1.7$ $p = 0.005$) and baseline intraventricular dyssynchrony index ($ß = -1.55$, $p = 0.007$). All other parameters were unable to predict reverse remodeling. A pre-implant QSm-QSt of 38 ms (+2 SDs from the mean of normal controls) separated responders from non-responders: all responders had a value > 38 ms and all non-responders had a value < 38 ms (Fig. 1). In a similar way a pre-implant intraventricular dyssynchrony index of 28 ms separated responders and non-responders: all responders had an index > 28 ms, all non-responders < 28 ms (Fig. 2). Sensitivity and specificity were both 100%.

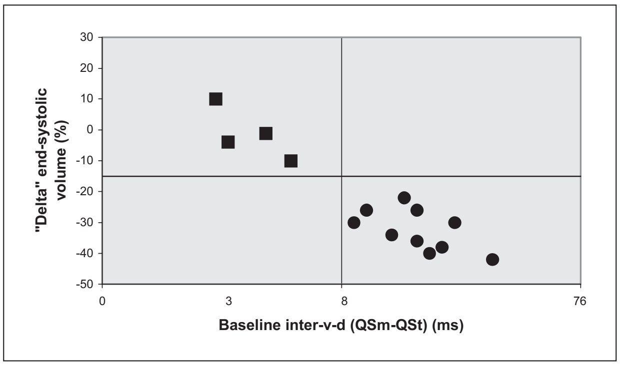

Figure 1. *Correlation between pre-implantation interventricular dyssynchrony and reverse remodeling after cardiac resynchronization therapy. inter-v-d = interventricular delay; QSm = interval between Q wave and tissue Doppler S wave on the mitral annulus; QSt = interval between Q wave and tissue Doppler S wave on the tricuspid annulus.* Circles: *responders;* squares: *non-responders.*

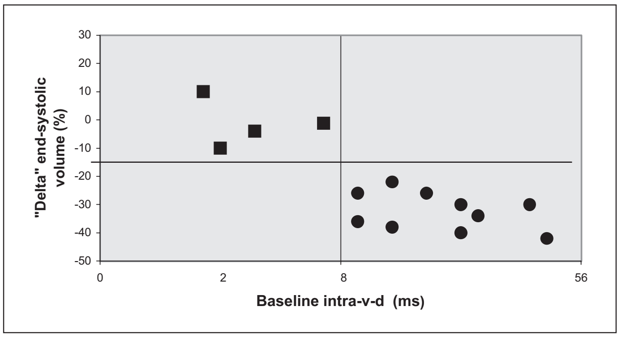

Figure 2. *Correlation between pre-implantation intraventricular dyssynchrony and reverse remodeling after cardiac resynchronization therapy. intra-v-d = intraventricular delay.* Circles: *responders;* squares: *non-responders.*

Discussion

In our experience biventricular pacing was a useful and safe tool to treat well-selected CHF patients who did not respond to optimal medical therapy. However, of concern is the fact that up to 30% of patients still do not respond to CRT[1,4]. The responders are patients in whom clinical and instrumental parameters show significant improvements after CRT. Hemodynamic parameters (cardiac index, ejection fraction, dP/dT, systolic and pulse pressure, wedge pressure) are usually evaluated soon after implantation; clinical and volumetric parameters are evaluated during follow-up. In our study we considered volumetric parameters: responders are patients with a reduction in LV end-systolic volume > 15% compared to baseline, a decrease that is defined "reverse remodeling"[6,7,10]. There is a good correlation between the reduction in LV volumes and the improvement in clinical-functional parameters[11]. One of the most remarkable problems with CRT is to find a simple and accurate way to establish if patients will or will not respond to biventricular pacing. We need predictive parameters of successful reverse remodeling to improve the cost-effectiveness of the procedure. Baseline QRS duration is considered by some authors as an indicative parameter for responders to CRT, others exclude this correlation; anyway there is a trend toward a wider baseline QRS duration in responders compared to non-responders[11-13]. The degree of QRS shortening after pacing seems to be a more useful indicator: greater the shortening, better the response to CRT. The problem, however, is that this parameter cannot be used before implantation to identify responders[12,13]. None of the other clinical-instrumental parameters studied (6-min walk test, quality of life, metabolic equivalents, peak oxygen consumption) was able to predict the reduction in LV volumes; a weak association was found between a severely depressed ejection fraction and severely enlarged volumes at baseline, and a more effective reverse remodeling[6]. Anyway, patients with extreme ventricular enlargement and an ejection fraction < 15-20% poorly respond to CRT[14]. Other studies identify in a massive mitral regurgitation a predictive parameter of poor response[5]. Another issue to consider is the influence of the LV lead location on CRT efficacy: it is known that anterior, anterolateral and great cardiac veins are "non-target" locations for LV lead because these sites are associated with an increased rate of non-responsiveness. However, some reports from the Italian InSync Registry (Ricci et al. 2003, unpublished data) suggest that location in "target" or "non-target" veins was associated with a similar increase in LV ejection fraction. In our population locations of the LV leads were: lateral vein (6 cases: 5 responders, 1 non-responder); posterior (3 cases: 1 responder, 1 non-responder, 1 died at follow-up); posterolateral (3 cases: 2 responders, 1 non-responder); anterior (2 cases: 1 responder, 1 non-responder); anterolateral (1 case: responder). Thus, in our population, the lateral vein location was associated with greater efficacy (83% of responders), while among the two anterior locations we had 1 responder and 1 non-responder, and the only case of anterolateral location was a responder. In our work the number of anterior and anterolateral locations was too small for a definitive opinion.

TDI is, at present, one of the most promising methods to determine potential responders before the commitment is made to implant a CRT device. Yu et al.[6] demonstrated that an index of intraventricular systolic dyssynchrony evaluated before implantation is able to distinguish responders from non-responders: reverse remodeling is only seen in patients with a higher degree of baseline dyssynchrony. Other authors recently described similar findings[9]. In our work we studied interventricular and intraventricular dyssynchrony, and our findings were that both indexes can help to select patients who are potential responders to CRT. Both the QSm-QSt time and the SD of the 12 LV segment QS time completely separate responders from non-responders.

Some authors state that intraventricular resynchronization (reachable with isolated LV pacing) is hemodynamically more important than interventricular one (reachable only with biventricular pacing)[15,16]. Others believe that interventricular resynchronization should be a primary objective and demonstrated how non-simultaneous pacing (LV anticipated with respect to right ventricular) could give better results compared to simultaneous stimulation[7,17].

In our opinion it is important to evaluate interventricular and intraventricular baseline dyssynchrony because both may be predictive of reverse remodeling. Moreover, both interventricular and intraventricular resynchronization should be achieved when using CRT to treat CHF. Further studies are necessary, anyway, to better examine the role of these and other potential predictive parameters to guide patient selection and to evaluate the outcome. By this way cost-effectiveness will further improve and the risk of unnecessary implantation will be reduced.

The main limitations of our work are: 1) the small number of patients, so that it is difficult to give a definitive opinion about the real utility of PW-TDI in this setting; 2) the short follow-up period; 3) we used PW-TDI to evaluate dyssynchrony and resynchronization (other authors used more sophisticated TDI analysis and softwares); 4) our analysis was a *post-hoc* analysis of a prospective clinical registry.

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