

# Echocardiographic changes after cardiac resynchronisation therapy

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## Abstract

**Background and aim:** The aim of this prospective study was to evaluate echocardiographic changes in clinical responders and nonresponders after 3 and 15 months of cardiac resynchronisation therapy (CRT).

**Methods:** Fifty eight patients in whom a biventricular system was implanted between 2005 and 2008 were followed up at 3 and at 15 months. Clinical and echocardiography parameters including intra- and interventricular dyssynchrony were assessed at baseline and after 3 and 15 months of CRT. Every patient in whom quality of life, New York Heart Association (NYHA) class and/or 6-minute walk test (6MWT) improved (improvement of  $\geq 1$  NYHA class, 6MWT by more than 10%), and who was neither in hospital for heart failure nor died for cardiac reasons, was categorised as a clinical responder.

**Results:** In the responders' group, we found a significant improvement of right ventricular systolic function and a decrease in the size of the right ventricle (RV) only after 15 months (tricuspid annular plane systolic excursion [TAPSE]  $17.8 \pm 4.0$  mm to  $19.4 \pm 3.7$  mm,  $p < 0.05$ , RV diameter  $29.3 \pm 5.0$  mm to  $27.8 \pm 4.2$  mm,  $p < 0.05$ ). Significant improvement of other monitored parameters occurred 3 months after CRT implantation: left ventricle (LV) end-diastolic diameter  $70.5 \pm 7.8$  mm to  $66.1 \pm 8.3$  mm,  $p < 0.001$ , LV ejection fraction  $22.0 \pm 5.4\%$  to  $27.1 \pm 9.8\%$ ,  $p < 0.05$ , pulmonary artery pressure (peak gradient of tricuspid regurgitation)  $37.1 \pm 14.8$  mm Hg to  $27.6 \pm 8.9$  mm Hg,  $p < 0.001$ , tricuspid regurgitation (grade)  $1.9 \pm 0.9$  to  $1.5 \pm 0.6$ ,  $p < 0.05$ , mitral regurgitation (grade)  $2.6 \pm 0.9$  to  $2.2 \pm 0.9$ ,  $p < 0.001$ , LV dP/dt max (peak positive rate of pressure rise [slope of mitral regurgitant jet])  $482.4 \pm 155.4$  mm Hg/s to  $981.2 \pm 654.5$  mm Hg/s,  $p < 0.001$ , velocity time integral (VTI) in LV outflow tract (LVOT)  $14.1 \pm 4.3$  cm to  $16.7 \pm 4.1$  cm,  $p < 0.001$ . In the group of nonresponders, only 2 parameters improved significantly: LV dP/dt max  $561.2 \pm 347.9$  mm Hg/s to  $1024.5 \pm 745.3$  mm Hg/s,  $p < 0.001$ , and LVOT VTI  $14.5 \pm 3.0$  cm to  $16.3 \pm 2.9$  cm,  $p < 0.001$ . Other echocardiographic parameters did not show any important changes, and no changes occurred between 3 and 15 months. On the contrary, after 15 months we saw significant progression of tricuspid regurgitation in nonresponders. In multivariate analysis, combination of baseline delay between time to peak systolic velocity in ejection phase at basal septal and basal lateral segments (Ts-lateral-septal delay) and serum creatinine was a strong predictor of clinical CRT response (area under curve was 0.80, percentage of correct decision was 82%).

**Conclusions:** In the group of responders, significant changes of most monitored echocardiographic parameters were observed 3 months after CRT implantation. The only parameters which changed significantly after 15 months, but not previously, were the systolic function of the RV and the decrease in the RV size. In the group of nonresponders, these changes were not observed.

**Key words:** cardiac resynchronisation therapy, heart failure, echocardiography, ventricular dyssynchrony

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## INTRODUCTION

Cardiac resynchronisation therapy (CRT) is an established treatment for patients with advanced chronic heart failure (HF)

with electromechanical delay. After this therapy, about two thirds of patients show improvement in HF symptoms and exercise capacity. Moreover, a decrease in rehospitalisation

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for HF and improved long-term survival compared to optimal medical therapy has been demonstrated [1–3].

Echocardiographically, it is possible to document the positive impact of CRT by the improvement of the function of the left ventricle (LV) [4–7], a decrease in mitral regurgitation [8] and absence of ventricular dyssynchrony.

Unfortunately, about one third of patients do not respond to CRT [9, 10]. The main factors which influence the final clinical impact are: absence of ventricular dyssynchrony before implantation or its persistence after implantation [10, 11], degree of remodelling of the LV, aetiology of LV dysfunction, presence of viable vs. nonviable myocardium (scar), position of electrodes, setting of AV delay and VV delay.

The aim of our prospective study was to evaluate echocardiographic changes in clinical responders and nonresponders after 3 and 15 months of CRT.

## METHODS

### Study group

The study involved 58 patients in whom a biventricular system (in 35 patients ICD + biventricular stimulation [BS], in 23 patients BS) was implanted between July 2005 and May 2008. The patients' mean age was  $67 \pm 9$  years. NYHA HF classifications were: NYHA IV (1 patient), NYHA III–IV (18 patients), NYHA III (23 patients), NYHA II–III (13 patients), NYHA II (3 patients), with average QRS duration  $193 \pm 33$  ms. Thirty three (57%) patients had ischaemic cardiomyopathy (ICM), 22 (38%) patients non-ischaemic cardiomyopathy (NICM), and 3 (5%) patients had both together (5%). In the group of responders were ICM vs. NICM (without coronary artery disease [CAD]) 47% vs. 47% ( $p = \text{NS}$ ) (concurrency of both 5%), and in the group of nonresponders were ICM vs. NICM 74% vs. 21% ( $p < 0.05$ ) (concurrency of both 5%). Baseline characteristics of CAD and history of revascularisation in responders and nonresponders are presented in Ta-

ble 1. In addition, 45 patients had either sinus rhythm or atrial stimulation and 13 patients suffered from permanent atrial fibrillation. Left bundle branch block (LBBB) was present in 38 patients, right bundle branch block (RBBB) and left anterior hemiblock in 1 patient, RBBB in 1 patient, and stimulated action (DDD/VVI mode) in 18 patients.

One day before implantation, and at 3 and 15 months after implantation, we assessed: NYHA class, quality of life (QOL) measured by the Minnesota Living with Heart Failure (MLHF) questionnaire, and the 6-minute walk test (6MWT).

### Echocardiographic examinations

All echocardiographic examinations were assessed by one specialist (R.P.). In addition to a standard echocardiographic examination using a SONOS 5500 Philips appliance, we assessed the longitudinal systolic function of the RV using tricuspid annular plane systolic excursion (TAPSE) by M-mode echocardiography from the apical 4-chamber view; sizes of right and left ventricles were measured from the parasternal long axis view; degrees of tricuspid and mitral regurgitation were assessed semiquantitatively with 1–4 scale; and pulmonary pressure was measured using peak gradient of tricuspid regurgitation (PG max TR). We also assessed the presence of interventricular mechanical dyssynchrony (IVMD) — interventricular delay as the difference between pre-ejection times of left and right ventricles (pulse Doppler record of flows in left and right ventricle outflow tract);  $\text{IVMD} \geq 40$  ms was considered to represent severe interventricular dyssynchrony. For assessing intraventricular dyssynchrony we used the following parameters: septal to posterior wall motion delay (SPWMD), with  $\text{SPWMD} \geq 130$  ms considered to represent severe intraventricular dyssynchrony (M-mode); left ventricular pre-ejection interval (LPEI); pulse Doppler record of flow in left ventricle outflow tract (LVOT), with  $\text{LPEI} \geq 140$  ms considered to represent severe intraventricular dyssynchrony; and

**Table 1.** Baseline characteristics of coronary artery disease and history of revascularisation in responders and nonresponders

	Responders (n = 38)	Nonresponders (n = 19)
Normal coronary angiography	18 (47%)	4 (21%)
Severity of coronary artery disease		
Single-vessel	7 (18%)	4 (21%)
Multivessel	13 (34%)	11 (58%)
Lesion morphology		
Mild (< 50% stenosis)	2 (5%)	3 (16%)
Moderate (50–70% stenosis)	3 (8%)	8 (42%)
Severe (> 70% stenosis)	15 (38%)	4 (21%)
Involvement of ramus circumflexus	0 (0%)	4 (21%)
History of revascularisation		
Percutaneous coronary intervention (PCI)	5 (13%)	2 (10%)
Coronary artery bypass grafting (CABG)	5 (13%)	6 (31%)
PCI with CABG	4 (10%)	1 (5%)

delay between time to peak systolic velocity in ejection phase at basal septal and basal lateral segments (Ts-lateral-septal delay), with Ts-lateral-septal delay  $\geq 65$  ms considered to represent severe intraventricular dyssynchrony. For non-invasive estimation of systolic output, we measured velocity time integral (VTI) in LVOT (average of 3 subsequent measurements). Contractility of the LV was assessed using  $dp/dt_{max}$  (slope of mitral regurgitant jet). Left ventricular ejection fraction (LVEF) was calculated from conventional apical 2- and 4-chamber images, using the biplane Simpson's technique.

### Additional examinations

We measured QRS duration by ECG record at a speed of 100 mm/s initially. All the patients had undergone coronary angiography during the previous 6 months. Coronary angiograms were obtained in multiple projections. Coronary artery stenosis was assessed in the left anterior descending artery, right coronary artery, left main artery, left circumflex artery, and ramus intermedius artery (if present). The severity of CAD (defined as mild [ $< 50\%$  stenosis], moderate [ $50\text{--}70\%$  stenosis], or severe [ $> 70\%$  stenosis in at least one major coronary artery]) and single-vessel involvement vs. multivessel involvement (multivessel involvement was defined as stenosis of any severity affecting more than one vessel) were noted.

Every patient in whom the QOL, NYHA class and/or 6MWT improved (improvement of  $\geq 1$  NYHA class, 6MWT by more than 10%), and who was neither in hospital for HF nor died for cardiac reasons, was categorised as a clinical responder.

### Statistical analysis

A statistical software package (SPSS 11.5) was used for all analyses. Numerical quantities are described by the average and standard deviation. We used t-test to process the data statistically for evaluating the differences between responders and

nonresponders. Next, two-way ANOVA with repeated measures (with Scheffé's post hoc test) was used to examine the differences in the responders and nonresponders. Levels of significance lower than 0.05 were considered statistically significant. All variables with a  $p < 0.15$  on univariate analysis were included in the logistic regression analysis. Odds ratios and 95% confidence interval (CI) were reported for all statistically significant variables at a  $p < 0.05$ . A receiver operating characteristic (ROC) curve for the assessment of the predictive value of baseline Ts-lateral-septal delay and serum creatinine in the responders and nonresponders was plotted and the area under curve (AUC) was calculated. In ROC curve analysis, the percentage of correct decision (PC) was calculated.

### RESULTS

After 15 months, 38 (66%) patients were marked as responders to CRT and 19 (33%) patients as clinical nonresponders. Between the third and fifteenth month after implantation, 2 patients died: 1 (the one who lacked ventricular dyssynchrony initially) died of refractory HF and was included in the group of nonresponders; and 1 patient (the one who suffered from ventricular dyssynchrony initially) whose health improved dramatically after the first 3 months, died of non-cardiac disease. In the group of nonresponders, 7 patients were hospitalised for decompensated HF during the 15-month follow-up. In 51 patients, intra- or interventricular dyssynchrony was present initially; 7 patients lacked ventricular dyssynchrony.

A comparison of the initial parameters (i.e. before implantation of the biventricular system) in responders and nonresponders showed that these two groups did not differ statistically dramatically in either initial clinical or basic echocardiographic parameters: NYHA class, QRS duration, QOL, 6MWT, LVEF, LVESD, LVEDD, or degree of mitral regurgitation (Table 2). Significant changes occurred in the relevance

**Table 2.** Comparison of initial clinical and echocardiographic parameters between responders and nonresponders

	Responders	Nonresponders	P
QRS [ms]	193.0 $\pm$ 28.3	195.4 $\pm$ 42.0	NS
NYHA class	2.9 $\pm$ 0.4	3.0 $\pm$ 0.4	NS
QOL score	49.0 $\pm$ 16.5	55.1 $\pm$ 18.9	NS
6MWT [m]	358.7 $\pm$ 98.4	371.5 $\pm$ 105.4	NS
LVEF [%]	22.0 $\pm$ 5.4	22.1 $\pm$ 6.9	NS
LVEDD [mm]	70.5 $\pm$ 7.8	72.0 $\pm$ 7.8	NS
LVESD [mm]	64.3 $\pm$ 9.0	65.6 $\pm$ 8.3	NS
MR [grade]	2.6 $\pm$ 0.9	2.4 $\pm$ 0.9	NS
TAPSE [mm]	17.8 $\pm$ 4.0	15.2 $\pm$ 3.1	$< 0.05$
RV [mm]	29.3 $\pm$ 5.0	30.4 $\pm$ 4.6	NS
LV $dp/dt_{max}$ [mm Hg/s]	482.4 $\pm$ 155.4	561.2 $\pm$ 348.0	NS
Creatinine ( $\mu\text{mol/L}$ )	110.8 $\pm$ 40.8	139.4 $\pm$ 52.2	$< 0.05$

QOL — quality of life; LVEF — left ventricular ejection fraction; LVEDD — left ventricular end-diastolic diameter; LVESD — left ventricular end-systolic diameter; MR — mitral regurgitation (grade 1–4); 6MWT — six-minute walk test; RV — right ventricle diameter; TAPSE — tricuspid annular plane systolic excursion; LV  $dp/dt_{max}$  — peak positive rate of pressure rise (slope of mitral regurgitant jet)

**Table 3.** Comparison of initial parameters of ventricular dyssynchrony and dP/dt of left ventricle in responders and nonresponders

	Responders	Nonresponders	P
IVMD [ms]	62.1 ± 23.1	46.8 ± 30.3	< 0.05
Ts-lateral-septal [ms]	71.2 ± 32.0	48.4 ± 29.2	< 0.05
LV-PEI [ms]	157.3 ± 42.2	146.6 ± 55.5	NS
SPWMD [ms]	213.2 ± 84.6	168.2 ± 122.3	NS
LV dP/dtmax [mm Hg/s]	482.4 ± 155.4	561.2 ± 348.0	NS

IVMD — interventricular mechanical delay; Ts-lateral-septal — delay between time to peak systolic velocity in ejection phase at basal septal and basal lateral segments; LV-PEI — left ventricular pre-ejection interval; SPWMD — septal to posterior wall motion delay; LV dP/dtmax — peak positive rate of pressure rise (slope of mitral regurgitant jet)

of longitudinal systolic dysfunction of the RV (in the nonresponders, the dysfunction was more significant), in the degree of interventricular dyssynchrony (in the responders, there were more significant signs of interventricular dyssynchrony) and in the degree of intraventricular dyssynchrony (Tables 2, 3). Other parameters evaluating the presence of intraventricular dyssynchrony did not show any significant changes, although the group of responders tended towards more serious signs of intraventricular dyssynchrony (Table 3). A significant difference also occurred in the serum creatinine, which was lower in the responders' group (Table 2).

Multivariate analysis showed increasing Ts-lateral-septal delay and serum creatinine as significant risk factors for responders and nonresponders among patients with CRT (Table 4). The area under the ROC curve for the Ts-lateral-septal delay and serum creatinine was 0.8 (Fig. 1, Table 5). The percentage of correct decisions was 82% (Table 5).

After 3 months, statistically important reductions of intra- and interventricular dyssynchrony occurred in both groups. Detailed analyses of both groups revealed that in responders, intra- and interventricular dyssynchrony was proved initially in all patients, whereas, in the group of nonresponders, there were 7 patients in whom no ventricular dyssynchrony was proved initially.

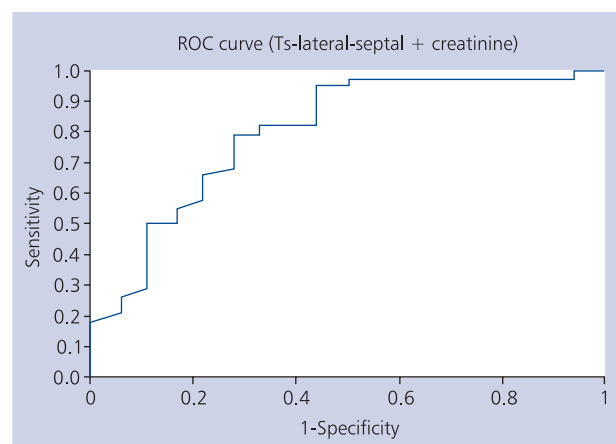
In the group of responders, we found that except for the RV parameters, in which we had significant improvement of systolic function and decreased size only after 15 months, other parameters (both clinical and echocardiographic) improved significantly after 3 months (Tables 6, 7). During the next follow-up (after 15 months), further improvement occurred in only 4 echocardiographic parameters: increase of LVEF, reduction of LVEDD, reduction of LVESD, and increase of LVOT VTI. Clinical and other echocardiographic parameters did not show any additional significant changes (Table 7).

In the group of nonresponders, only 2 parameters improved significantly: LV dP/dtmax and LVOT VTI. Other echocardiographic and clinical parameters did not show any important changes, and no changes occurred between 3 and 15 months. On the contrary, after 15 months we saw significant progression of tricuspid regurgitation in nonresponders.

**Table 4.** Multivariate analysis of risk factors for responders and nonresponders

Independent variable	Odds ratio (95% CI)	P
TAPSE [mm]	1.10 (0.87–1.40)	0.42
IVMD [ms]	1.00 (0.97–1.03)	0.83
Ts-lateral-septal [ms]	1.04 (1.00–1.08)	0.03
Creatinine [μmol/L]	0.97 (0.94–0.99)	0.02

CI — confidence interval; TAPSE — tricuspid annular plane systolic excursion; IVMD — interventricular mechanical delay



**Figure 1.** The baseline Ts-lateral-septal delay and serum creatinine have been found to be important factors influencing responders and nonresponders. The area under the ROC curve for the Ts-lateral-septal delay and serum creatinine was 0.8

Changes in selected echocardiographic parameters in responders and nonresponders are presented in Table 7.

### DISCUSSION

Cardiac resynchronisation therapy first appeared about 10 years ago and is evidently a very effective nonpharmacological medical treatment in certain patients suffering from HF. However, approximately one third of patients do not experience the benefit of CRT [9, 10]. One of the main causes of

**Table 5.** ROC curve analysis of risk factors to predict responders and nonresponders

Variable	Cutoff <sup>a</sup>	AUC	PC [%]
TAPSE [mm]	> 13	0.69	60
IVMD [ms]	> 23	0.66	71
Ts-lateral-septal [ms]	> 29	0.68	69
Creatinine [ $\mu\text{mol/L}$ ]	< 174	0.68	71
Composite panel <sup>b</sup>	Ts lateral septal – 0.6556 * Creatinine > –45	0.80	82

<sup>a</sup>Cutoff value for cardiac resynchronisation therapy responders; <sup>b</sup>Results were generated using model including Ts-lateral septal and creatinine; TAPSE — tricuspid annular plane systolic excursion; IVMD — interventricular mechanical delay; AUC — area under curve; PC — percentage of correct decisions

**Table 6.** Clinical changes after 3 and 15 months in the group of responders

	Initially	After 3 months	P	After 15 months	P
NYHA class	2.9 $\pm$ 0.4	1.9 $\pm$ 0.4	< 0.001	1.8 $\pm$ 0.5	< 0.001
QOL [score]	49.0 $\pm$ 16.5	26.5 $\pm$ 15.1	< 0.001	26.4 $\pm$ 12.9	< 0.001
6MWT [m]	358.7 $\pm$ 98.4	436.0 $\pm$ 93.0	< 0.001	449.8 $\pm$ 97.7	< 0.001

NYHA — New York Heart Association; QOL — quality of life; 6MWT — six-minute walk test

**Table 7.** Echocardiographic changes after 3 and 15 months in the group of responders (resp.) and nonresponders (nonresp.)

	Initially	After 3 months	P	After 15 months (initially vs. after 15 months)	P
LVEF resp. [%]	22.0 $\pm$ 5.4	27.1 $\pm$ 9.8	< 0.05	32.8 $\pm$ 12.5	< 0.001
LVEF nonresp. [%]	22.1 $\pm$ 6.9	23.6 $\pm$ 8.7	NS	24.8 $\pm$ 8.4	NS
LVEDD resp. [mm]	70.5 $\pm$ 7.8	66.1 $\pm$ 8.3	< 0.001	64.0 $\pm$ 8.1	< 0.001
LVEDD nonresp. [mm]	72.0 $\pm$ 7.8	70.7 $\pm$ 8.2	NS	69.6 $\pm$ 9.8	NS
LVESD resp. [mm]	64.3 $\pm$ 9.0	59.4 $\pm$ 9.5	< 0.001	55.7 $\pm$ 10.8	< 0.001
LVESD nonresp. [mm]	65.6 $\pm$ 8.3	63.7 $\pm$ 9.4	NS	64.2 $\pm$ 9.4	NS
RV resp. [mm]	29.3 $\pm$ 5.0	28.2 $\pm$ 4.8	NS	27.8 $\pm$ 4.2	< 0.05
RV nonresp. [mm]	30.4 $\pm$ 4.6	29.8 $\pm$ 4.9	NS	30.6 $\pm$ 5.9	NS
TAPSE resp. [mm]	17.8 $\pm$ 4.0	18.4 $\pm$ 3.8	NS	19.4 $\pm$ 3.7	< 0.05
TAPSE nonresp. [mm]	15.2 $\pm$ 3.1	16.2 $\pm$ 3.9	NS	15.6 $\pm$ 3.1	NS
TR max PG resp. [mm Hg]	37.1 $\pm$ 14.8	27.6 $\pm$ 8.9	< 0.001	26.4 $\pm$ 9.0	< 0.001
TR max PG nonresp. [mm Hg]	35.3 $\pm$ 12.8	31.5 $\pm$ 12.2	NS	32.7 $\pm$ 12.7	NS
TR resp. [grade]	1.9 $\pm$ 0.9	1.5 $\pm$ 0.6	< 0.05	1.7 $\pm$ 0.8	< 0.05
TR nonresp. [grade]	1.9 $\pm$ 1.1	2.1 $\pm$ 1.1	NS	2.3 $\pm$ 1.2	< 0.001
MR resp. [grade]	2.6 $\pm$ 0.9	2.2 $\pm$ 0.9	< 0.001	2.3 $\pm$ 0.9	< 0.001
MR nonresp. [grade]	2.4 $\pm$ 0.9	2.1 $\pm$ 0.9	NS	2.4 $\pm$ 1.1	NS
LVOT VTI resp. [cm]	14.1 $\pm$ 4.3	16.7 $\pm$ 4.1	< 0.001	18.7 $\pm$ 4.4	< 0.001
LVOT VTI nonresp. [cm]	14.5 $\pm$ 3.0	16.3 $\pm$ 2.9	< 0.001	17.8 $\pm$ 2.7	< 0.001
LV dP/dt max resp. [mm Hg/s]	482.4 $\pm$ 155.4	981.2 $\pm$ 654.5	< 0.001	1,014.9 $\pm$ 495.3	< 0.001
LV dP/dt max nonresp. [mm Hg/s]	561.3 $\pm$ 347.9	1,024.5 $\pm$ 45.3	< 0.001	871.5 $\pm$ 349.3	< 0.001

RV — right ventricle diameter; TAPSE — tricuspid annular plane systolic excursion; TR max PG — peak gradient of tricuspid regurgitation; TR — tricuspid regurgitation (grade 1–4); MR — mitral regurgitation (grade 1–4); LVEF — left ventricular ejection fraction; LVEDD — left ventricular end-diastolic diameter; LVESD — left ventricular end-systolic diameter; LVOT VTI — velocity time integral in left ventricle outflow tract; LV dP/dtmax — peak positive rate of pressure rise (slope of mitral regurgitant jet)

such failure is the absence of significant ventricular dyssynchrony. Initial studies, which in most cases were reported by a single centre, involved relatively small numbers of patients

and assessed the significance of ventricular dyssynchrony for determining responders to CRT. All in all, they showed that echocardiographic quantification of ventricular dyssynchro-



ny predicts responders with good sensitivity and specificity, and that echocardiographic confirmation of ventricular dyssynchrony enables the distinction of responders from nonresponders to CRT in more detail than QRS duration on ECG [10–14]. The necessity to examine ventricular dyssynchrony echocardiographically was suggested by the first multicentre study, PROSPECT [15]. That study's objective was to test 12 echocardiographic parameters used for quantification of mechanical dyssynchrony; it concluded that the tested echocardiographic parameters did not reliably distinguish responders from nonresponders.

In our study, we corroborated several conclusions with previously published findings of both larger and smaller studies [4, 10, 16, 17]. For example, there were a similar number of responders and nonresponders. Further, responders and nonresponders initially differed significantly in the degree of ventricular dyssynchrony, in the severity of systolic dysfunction of the RV measured by TAPSE, and also in renal insufficiency [18]. In the group of responders, there were initially more serious signs of IVMD (the study CARE HF [19]). Our analysis also confirmed the importance of evaluating IVMD for the estimation of the impact of CRT as reported by Stockburger et al. [20]. We also confirmed the more serious signs of intraventricular dyssynchrony measured by Ts-lateral-septal parameter as reported by Bax et al. [10]. Ghio et al. [21] observed that TAPSE has a strong predictive value in patients with HF and that a low TAPSE value is likely to be a marker of a severe stage of HF. Concordantly, we observed that the group of clinical responders had a significantly higher TAPSE value than the group of nonresponders initially.

In the group of responders, we found significant improvement of RV systolic function and also significant RV remodelling only after 15 months of CRT; on the contrary we observed significant improvement of LV systolic function and remodelling after only 3 months.

We consider the improvement of the RV systolic function to be multifactorial and a long-term process including improvement of LV systolic function and remodelling of the LV, decreases in mitral regurgitation and pulmonary artery pressure, and improvement in RV diastolic function after CRT [22]. The main predictor of systolic functional improvement was the degree of ventricular dyssynchrony before implantation of CRT; the same conclusion was reached by Bleeker [23], who found that a significant decrease in the size of both ventricles occurred only in those patients with significant ventricular dyssynchrony initially.

Another important conclusion is that 7 of our patients, in whom the existence of ventricular dyssynchrony was not present initially, were not categorised as responders (1 patient died of refractory HF between the third and fifteenth month), in line with the study by Bax et al. [10]. These 7 patients had relatively wide QRS complexes (150–168 ms) initially and at the same time lacked ventricular dyssynchro-

ny (as shown in the study by Bader et al. [24]). From a number of studies, it is obvious that QRS duration is neither a convenient indicator of dyssynchrony nor of the effects of CRT [24, 25].

More detailed analysis of 12 additional nonresponders, in whom the signs of ventricular dyssynchrony were confirmed initially, revealed other possible predictors of a nonresponder to CRT, as published in previous studies. Ischaemic heart disease ranks among them [19], and it was present in 9 patients (in our group of nonresponders there were more patients with ICM). In the available literature we did not find a study in which all patients underwent not only detailed echocardiography but also coronarography during the 6 months before implantation of CRT.

We find it extremely interesting that in the group of responders there was no haemodynamically significant involvement of ramus circumflexus (RC) or its branches, nor of its prior successful revascularisation using percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery. In nonresponders, on the contrary, we found significant involvement of RC or its branches in 4 patients (total or subtotal closure). Because the RC supplies the posterolateral wall of the LV, there is likely to be permanent ischaemia in this area, which might have contributed to the suboptimal response to CRT.

Additional negative predictors mentioned in the literature and also present in our nonresponders are: significant mitral regurgitation in 3 patients and LVEDD  $\geq$  75 mm in 3 patients [7]. Signs of ventricular dyssynchrony continued in 5 patients after implantation of CRT [11], and suboptimal position of the LV electrodes was observed in 4 patients. Two patients had echocardiographic confirmation of the scar in the posterolateral wall of the LV [26]. Continuing alcoholism was confirmed in 1 patient. Two patients showed signs of renal insufficiency with creatinine greater than 190  $\mu$ mol/L [27]. Eleven of these 12 patients showed a combination of 2 or more of the abovementioned negative factors.

Finally, we documented that responders showed a significant improvement in most of the measured parameters (both clinical and echocardiographic) after 3 months; this finding agrees with some of the published studies (e.g. the MIRACLE study [4]). The only parameters which changed significantly only after 15 months were: improvement of RV systolic function and decrease of RV size.

Our study was limited by the small number of patients and by not using some of the latest echocardiographic methods to quantify ventricular dyssynchrony (e.g. speckle tracking). Another limitation was that we did not use the 'gold standard' for assessing RV function and morphology or for assessing LV reverse remodelling.

## CONCLUSIONS

Fifteen months after CRT implantation, we observed significant improvement of systolic function and also significant re-

modelling of both ventricles in the group of responders. In multivariate analysis, combination of baseline Ts-lateral-septal delay and serum creatinine was a strong predictor of clinical CRT response (AUC = 0.80, PC = 82%).

We find it significant that none of the 7 patients in whom ventricular dyssynchrony was not initially confirmed were responders.

Another important finding is the fact that in the group of responders, most of the monitored echocardiographic parameters showed significant improvement within only 3 months after CRT. The only parameters which changed significantly only after 15 months were the systolic function of the RV and the decrease in its size. In the group of non-responders, these changes were not observed; on the contrary, there was significant progression of tricuspid regurgitation 15 months after CRT.

When we compared all the initial clinical and echocardiographic parameters, we found that the two groups differed significantly not only in the degree of ventricular dyssynchrony and baseline creatinine, but also in the severity of systolic dysfunction of the RV measured by TAPSE.

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**Conflict of interest:** none declared

### References

- Bristow MR, Saxon LA, Boehmer J et al. Cardiac-resynchronization therapy with or without implantable defibrillator in advanced chronic heart failure. *N Engl J Med*, 2004; 350: 2140–2150.
- Cleland JG, Daubert JC, Erdmann E et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med*, 2005; 352: 1539–1549.
- Cleland JG, Daubert JC, Erdmann E et al. Long-term effect of cardiac resynchronization on morbidity and mortality in heart failure (CARE-HF trial extension phase). *Eur Heart J*, 2006; 27: 1928–1932.
- Abraham WT, Fischer WG, Smith AL et al.; MIRACLE Study Group. Multicenter InSync Randomized Clinical Evaluation. Cardiac resynchronization in chronic heart failure. *N Engl J Med*, 2002; 346: 1845–1853.
- Bordachar P, Lafitte S, Reuter S et al. Echocardiographic parameters of ventricular dyssynchrony validation in patients with heart failure using sequential biventricular pacing. *J Am Coll Cardiol*, 2004; 44: 2157–2165.
- Linde C, Leclercq C, Rex S et al. Long-term benefits of biventricular pacing in progressive heart failure: results from the MULTIsite STimulation in cardiomyopathy (MUSTIC) Study. *J Am Coll Cardiol*, 2002; 40: 111–118.
- Diaz-Infante E, Mont L, Leal J et al. Predictors of lack of response to resynchronization therapy. *Am J Cardiol*, 2005; 95: 1436–1440.
- Breithardt OA, Sinha AM, Schwammenthal E et al. Acute effects of cardiac resynchronization therapy on functional mitral regurgitation in advanced systolic heart failure. *J Am Coll Cardiol*, 2003; 41: 765–770.
- Gorcsan J 3rd, Tanabe M, Bleeker GB et al. Combined longitudinal and radial dyssynchrony predicts ventricular response after cardiac resynchronization therapy. *J Am Coll Cardiol*, 2007; 50: 1476–1483.
- Bax JJ, Bleeker GB, Marwick TH et al. Left ventricular dyssynchrony predicts response and prognosis after cardiac resynchronization therapy. *J Am Coll Cardiol*, 2004; 44: 1834–1840.
- Bleeker G, Mollema S, Holman E et al. Left ventricular resynchronization is mandatory for response to cardiac resynchronization therapy. *Circulation*, 2007; 116: 1440–1448.
- Bax JJ, Molhoek SG, Marwick TH et al. Usefulness of myocardial tissue Doppler echocardiography to evaluate left ventricular dyssynchrony before and after biventricular pacing in patients with idiopathic dilated cardiomyopathy. *Am J Cardiol*, 2003; 91: 94–97.
- Penicka M, Bartunek J, De Brune B et al. Improvement of left ventricular function after cardiac resynchronization therapy is predicted by tissue doppler imaging echocardiography. *Circulation*, 2004; 109: 978–983.
- Yu CM, Fung JW, Zhang Q et al. Tissue doppler imaging is superior to strain rate imaging and postsystolic shortening on the prediction of reverse remodeling in both ischemic and nonischemic heart failure after cardiac resynchronization therapy. *Circulation*, 2004; 110: 66–73.
- Chung ES, Leon AR, Tavazzi L et al. Results of the predictors of response to CRT (PROSPECT) Trial. *Circulation*, 2008; 117: 2608–2616.
- Mollema S, Bleeker G, van der Wall E et al. Usefulness of QRS duration to predict response to cardiac resynchronization therapy in patients with end-stage heart failure. *Am J Cardiol*, 2007; 100: 1665–1670.
- Szulik M, Stabryla-Deska J, Boidol J et al. Echocardiography-based qualification and response assessment to cardiac resynchronization therapy in patients with chronic heart failure. The matrix metalloproteinase-9 substudy. *Kardiologia Pol*, 2011; 69: 1043–1051.
- Van Bommel R, Mollema S, Borleffs C et al. Impaired renal function is associated with echocardiographic nonresponse and poor prognosis after cardiac resynchronization therapy. *J Am Coll Cardiol*, 2011; 57: 549–555.
- Ghio S, Freemantle N, Scelsi L et al. Long-term left ventricular reverse remodelling with cardiac resynchronization therapy: results from the CARE-HF trial. *Eur J Heart Fail*, 2009; 11: 480–488.
- Stockburger M, Fateh-Moghadam S, Nitardy A et al. Baseline Doppler parameters are useful predictors of chronic left ventricular reduction in size by cardiac resynchronization therapy. *Europace*, 2008; 10: 69–74.
- Ghio S, Recusani F, Klersy C et al. Prognostic usefulness of the tricuspid annular plane systolic excursion in patients with congestive heart failure secondary to idiopathic or ischemic dilated cardiomyopathy. *Am J Cardiol*, 2000; 85: 837–842.
- Voelkel NF, Quaife RA, Leinwand LA et al. Right ventricular function and failure: report of a National Heart, Lung and Blood Institute working group on cellular and molecular mechanisms of right heart failure. *Circulation*, 2006; 114: 1883–1891.
- Bleeker G, Schalij M, Nihoyannopoulos P et al. Left ventricular dyssynchrony predicts right ventricular remodeling after cardiac resynchronization therapy. *J Am Coll Cardiol*, 2005; 46: 2264–2269.
- Bader H, Garrique S, Lafitte S et al. Intra-left ventricular electromechanical asynchrony. A new independent predictor of severe cardiac events in heart failure patients. *J Am Coll Cardiol*, 2004; 43: 248–256.
- Ghio S, Constantin C, Klersy C et al. Interventricular and intraventricular dyssynchrony are common in heart failure patients, regardless of QRS duration. *Eur Heart J*, 2004; 25: 571–578.
- Ypenburg C, Schalij M, Bleeker G et al. Impact of viability and scar tissue on response to cardiac resynchronization therapy in ischaemic heart failure patients. *Eur Heart J*, 2007; 28: 33–41.
- Shalaby A, El-Saed A, Voigt A et al. Elevated serum creatinine at baseline predicts poor outcome in patients receiving cardiac resynchronization therapy. *Pacing Clin Electrophysiol*, 2008; 31: 575–579.

# Zmiany echokardiograficzne u chorych poddanych terapii resynchronizującej

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## Streszczenie

**Wstęp i cel:** Niniejsze prospektywne badanie przeprowadzono w celu oceny echokardiograficznych zmian u chorych odpowiadających i nieodpowiadających na terapię resynchronizującą (CRT) po 3 i 15 miesiącach od wszczęcia urządzenia resynchronizującego.

**Metody:** Do badania włączono 58 chorych, u których wszczepiono urządzenie do stymulacji dwukomorowej w okresie od 7/2005 do 5/2008. Stan kliniczny uczestników badania i parametry echokardiograficzne, w tym dyssynchronię śród- i międzykomorową, oceniano wyjściowo, a następnie po 3 i 15 miesiącach od wszczęcia CRT. Za osoby odpowiadające na terapię resynchronizującą uznano wszystkich chorych, u których stwierdzono poprawę w zakresie jakości życia, klasy NYHA i/lub wyniku testu 6-minutowego marszu (6MWT) (poprawa klasy NYHA o  $\geq 1$ , poprawa 6MWT o ponad 10%) i którzy nie byli hospitalizowani z powodu niewydolności serca ani nie umarli z przyczyn sercowo-naczyniowych.

**Wyniki:** W grupie chorych reagujących na CRT stwierdzono istotną poprawę czynności skurczowej i zmniejszenie wielkości prawej komory (RV) po 15 miesiącach [zwiększenie wychylenia płaszczyzny pierścienia zastawki trójdzielnej w skurczu (TAPSE) z  $17,8 \pm 4,0$  mm do  $19,4 \pm 3,7$  mm,  $p < 0,05$ ; zmniejszenie wymiaru RV z  $29,3 \pm 5,0$  mm do  $27,8 \pm 4,2$  mm;  $p < 0,05$ ]. Inne parametry uległy istotnej poprawie już po 3 miesiącach po wszczęciu CRT [późnorozkurczowy wymiar lewej komory (LV) z  $70,5 \pm 7,8$  mm do  $66,1 \pm 8,3$  mm;  $p < 0,001$ ; frakcja wyrzutowa LV z  $22,0 \pm 5,4\%$  do  $27,1 \pm 9,8\%$ ;  $p < 0,05$ ; ciśnienie w tętnicy płucnej (maksymalny gradient fali niedomykalności trójdzielnej) z  $37,1 \pm 14,8$  mm Hg do  $27,6 \pm 8,9$  mm Hg,  $p < 0,001$ ; niedomykalność trójdzielna (stopień) z  $1,9 \pm 0,9$  do  $1,5 \pm 0,6$ ;  $p < 0,05$ ; niedomykalność mitralna (stopień) z  $2,6 \pm 0,9$  do  $2,2 \pm 0,9$ ;  $p < 0,001$ ; LV dp/dt max — maksymalna szybkość narastania ciśnienia (spektrum niedomykalności mitralnej) z  $482,4 \pm 155,4$  mm Hg/s do  $981,2 \pm 654,5$  mm Hg/s;  $p < 0,001$ , cała spektrum prędkości przepływu (VTI) w drodze odpływu lewej komory (LVOT) z  $14,1 \pm 4,3$  cm do  $16,7 \pm 4,1$  cm;  $p < 0,001$ ]. W grupie chorych nieodpowiadających na CRT tylko dwa parametry uległy znamiennej poprawie: LV dp/dt max z  $561,2 \pm 347,9$  mm Hg/s do  $1024,5 \pm 745,3$  mm Hg/s;  $p < 0,001$  i LVOT VTI z  $14,5 \pm 3,0$  cm do  $16,3 \pm 2,9$  cm;  $p < 0,001$ . Nie odnotowano istotnych zmian innych parametrów echokardiograficznych. Nie stwierdzono również żadnych zmian w okresie od 3. do 15. miesiąca po implantacji. Z kolei po 15 miesiącach zaobserwowano istotną progresję niedomykalności trójdzielnej u osób nieodpowiadających na CRT. W analizie wielu zmiennych czynnikami o dużej wartości predykcyjnej w ocenie klinicznej odpowiedzi na CRT (pole pod krzywą 0,80; odsetek właściwych decyzji 82%) były: występowanie różnicy czasów do szczytu fali skurczowej prędkości w fazie wyrzutowej podstawnych segmentów ściany bocznej i przegrody międzykomorowej (*Ts-lateral-septal delay*) i stężenia kreatyniny w surowicy podczas wyjściowej oceny uczestników.

**Wnioski:** W grupie chorych odpowiadających na CRT stwierdzono istotną poprawę większości monitorowanych parametrów echokardiograficznych już 3 miesiące po wszczęciu urządzenia resynchronizującego. Parametrami, które uległy istotnej poprawie dopiero po 15 miesiącach, były czynność skurczowa RV i zmniejszenie wielkości RV. W grupie chorych nieodpowiadających na CRT nie zaobserwowano powyższych zmian.

**Słowa kluczowe:** terapia resynchronizująca, niewydolność serca, echokardiografia, desynchronizacja komór

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