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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Predictors of functional mitral regurgitation improvement during a short-term follow-up after cardiac resynchronisation therapy

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Abstract

Background and aim: The study was undertaken to assess the predictive role of myocardial contractile reserve for functional mitral regurgitation (FMR) improvement after cardiac resynchronisation therapy (CRT), and to define other predictors of FMR improvement (FMRI) and the impact of FMRI on left ventricular (LV) reverse remodelling.

Methods and results: Among 90 patients in whom echocardiography was performed one day before and six weeks after CRT implantation, 66 with at least FMR(2+) in a four-point scale (mean age 64 ± 10 years, mean LV ejection fraction [LVEF] 25.7 ± 6%, ischaemic aetiology 48%) were included. FMRI was defined as the reduction of the FMR severity by at least one grade. The patients were divided into groups: A with FMRI (n = 30) and B without FMRI (n = 36). Contractile reserve was evaluated using low-dose dobutamine stress-echo before CRT implantation and was defined as a relative improvement in LVEF of more than 20% and segmental contractility improvement. Reverse remodelling was defined as the reduction of the LV end-systolic volume (LVESV) by at least 15%. Cox regression multivariate analysis revealed the following predictors for FMRI: contractile reserve preserved in more than three segments with an OR = 5.7 (95% CI 1.81–17.97, p = 0.005, sensitivity 65.5%, specificity 72.2%, AUC = 0.727) and LV end-diastolic diameter ≤ 74 mm with an OR = 2.09 (95% CI 0.75–5.78, p < 0.05, sensitivity 80.0%, specificity 47.2%, AUC = 0.632). FMRI was associated with greater reduction of LVESV (p = 0.002), greater increase in LVEF (p < 0.001) and higher incidence of the LV reverse remodelling (p < 0.001).

Conclusions: Preserved contractile reserve and lesser degree of LV dilation were predictive factors of short-term FMR improvement after CRT implantation. FMR improvement was associated with higher incidence of the LV reverse remodelling early, already in the six weeks after CRT implantation.

Key words: cardiac resynchronisation therapy, functional mitral regurgitation, dobutamine stress echocardiography, myocardial contractile reserve, reverse remodelling in heart failure

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INTRODUCTION

Cardiac resynchronisation therapy (CRT) is an established treatment option for patients with advanced chronic heart failure and prolonged QRS duration. The outcome of CRT is determined by a number of factors, and the improvement of functional mitral regurgitation (FMR) is one of the mechanisms behind the beneficial effect of the treatment [1, 2].

Significant FMR has important prognostic implications and is associated with a relatively high morbidity and mortality [3]. FMR caused by dilation, altered geometry, and systolic dysfunction of the left ventricle (LV) can itself promote progressive remodelling in the course of ischaemic or non-ischaemic dilated cardiomyopathy [4, 5]. This results in a vicious circle, with both LV dilatation and FMR acting as self-perpetuating processes. CRT may contribute to the reduction of FMR and reversing LV dilation [6, 7].

Functional mitral regurgitation, observed in patients with ischaemic and non-ischaemic cardiomyopathy, results from an imbalance between LV closing forces and mitral valve tethering forces, and resultant deformation of mitral valve geometry [2, 8]. FMR improvement (FMRI) after CRT implantation is a multistage process being modulated by an array of factors [2, 9]. The immediate decrease in FMR severity is a result of better coordination of ventricular contraction, including activation of resynchronised papillary muscles; this is reflected by the improvement of systolic function (i.e. the closing forces) and reduction of mitral leaflet tethering forces [2, 10]. Later reduction of FMR is probably mainly a result of the LV reverse remodelling and changes in the geometry of mitral apparatus [2, 9]. This latter effect is generally believed to develop at mid- and long-term follow-up, i.e. months after CRT implantation [2, 6, 7, 9].

It is noteworthy that the outcome of CRT is related to myocardial contractile reserve and viability in the paced left ventricular region [11]. Myocardial viability can be examined with several validated techniques, applied in ischaemic and non-ischaemic cardiomyopathy. Contractile reserve assessed by means of a widely available low-dose dobutamine stress-echo (LDSE) has high sensitivity and specificity [11–14].

Little is known about the predictors of FMRI after CRT implantation in short-term observation. While the role of preserved contractile reserve as a predictor of post-CRT clinical improvement and the LV reverse remodelling is well documented, its predictive value with regards to FMRI is unclear. The aim of this study was to define the predictors of FMRI and to evaluate the impact of FMRI on the incidence of LV reverse remodelling during six-week follow-up after CRT implantation.

METHODS

Patients

This study is a sub-analysis of the multicentre Myocardial Viability in Cardiac Resynchronisation Therapy (ViaCRT) trial [14]. A total of 90 out of the 129 consecutive patients with ischaemic and non-ischaemic LV dysfunction, who underwent CRT, were subjected to Doppler echocardiography one day prior to CRT implantation and six weeks thereafter. Sixty-six out of the 90 patients, presenting with more than mild FMR at baseline (FMR ≥ 2+) (mean age 64 ± 10 years, mean LV ejection fraction [LVEF] 25.7 ± 6%, ischaemic aetiology 48%) were included in this sub-analysis. The inclusion criteria for CRT were in line with the current guidelines, i.e. the evidence of systolic dysfunction with LVEF ≤ 35% despite optimal pharmacotherapy, New York Heart Association (NYHA) class II–IV, and QRS duration ≥ 120 ms. Patients with morphological abnormalities of the mitral valve, clinical or echocardiographic evidence for other structural cardiac diseases, and greater than mild aortic regurgitation were excluded.

Clinical assessment

As well as the echocardiographic evaluation, the clinical status of the patients was determined at the baseline and six weeks after CRT; the examination included determination of NYHA class, medication, and electrocardiogram (ECG) recording.

Echocardiography

A standard transthoracic echocardiographic examination was performed at rest and during LDSE. This included the acquisition of optimised grey-scale imaging data sets and spectral Doppler flows as well as myocardial velocity data. The following parameters were included into the analysis: LV internal dimensions in end-diastole (LVEDD) and end-systole (LVESD) that were measured from parasternal long-axis view two-dimensional (2D) images; LV volumes: LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), and LVEF that were measured using the 2D Simpson method. Doppler myocardial imaging velocity data were recorded using a colour-coded technique with two opposing LV walls adjusted sector width and optimal depth of imaging in apical views. Parameters of dyssynchrony were evaluated at baseline and six weeks after CRT implantation. Dyssynchrony was defined by tissue Doppler imaging as the maximum difference of time to onset of systolic velocity for six segments at basal level. Inter-ventricular delay (IVD) was calculated as the difference between the left ventricular and right ventricular pre-ejection periods from pulsed wave Doppler velocity images of corresponding outflow tracts. LV diastolic filling time (DFT) in relation to cardiac cycle length (R-R) was measured by transmitral pulsed wave Doppler and expressed as percentage of: DFT/R-R.

The severity of FMR was estimated semi-quantitatively from colour-flow Doppler images; an integrative approach was used, with measurements of vena contracta (VC) and mitral regurgitation jet to left atrial area ratio (MR/LA area) on a four-point scale on which FMR(1+) corresponded to MR/LA area less than 10% and/or VC less than 3 mm, FMR(2+)

to MR/LA area between 10% and 20% and/or VC 3 mm, FMR(3+) to MR/LA area greater than 20% but no more than 40% and/or VC greater than 3 mm and no more than 7 mm, and FMR(4+) to MR/LA area greater than 40% and/or VC greater than 7 mm.

A standard LDSE (up to 20 μg/kg/min) was performed prior to CRT implantation. Detailed analysis of segmental contractility improvement was conducted. The conventional 16-segment LV model was used to characterise contraction by the wall motion score index (WMSI). Each of the segments was analysed individually in multiple echocardiographic views on the basis of systolic thickening and motion. The segment function was scored as normal = 1, hypokinetic = 2, akinetic = 3, or dyskinetic/aneurysmatic = 4. WMSI was calculated as the sum of all the scores divided by the number of visualised segments. More than 20% improvement in WMSI ($\downarrow\Delta$WMSI > 20%) or more than 20% improvement in LVEF ($\uparrow\Delta$LVEF > 20%) from baseline to peak stress was considered significant to detect preserved contractile reserve.

Functional mitral regurgitation improvement was defined as the reduction of the FMR severity by at least one grade.

Reverse remodelling was defined as the reduction of the LVESV by at least 15% ($\downarrow\Delta$LVESV ≥ 15%). Moreover, the LVEF measurements were included into the analysis of the CRT effect on myocardial contraction from baseline through follow-up.

Statistical analysis

Normally distributed continuous variables were expressed as mean ± standard deviation (SD) unless otherwise indicated. Dichotomous data was expressed as percentages. The two-tailed paired and unpaired Student's t-tests were used for intragroup and intergroup comparisons of continuous variables, respectively. Categorical data were compared using Fisher's exact test or Pearson's χ^2 test. Correlations between continuous variables were analysed with a simple regression test. Cox regression multivariable analysis model was used to identify the independent predictors of FMRI. Receiver-operating characteristic (ROC) curves were obtained for quantitative variables that differed significantly between the two analysed groups, in order to calculate the cutoff values that most accurately predicted FMRI. The optimal cutoff was defined as a value with maximum sum of sensitivity and specificity. The results of all the tests were considered significant at p-value < 0.05. All the analyses were performed with STATISTICA v. 10.0 software.

RESULTS

Distribution of FMR severity and study groups

Eight out of 90 (9%) patients lacked echocardiographic evidence of FMR at the baseline. FMR(1+) was detected in 16/90 (18%) patients, FMR(2+) in 26/90 (29%) patients, FMR(3+) in 29/90 (32%) patients, and FMR(4+) in 11/90 (12%) patients. Therefore, a total of 24 (27%) patients presented with no or mild FMR at the baseline, and 66 patients showed at least FMR(2+). Severe FMR, corresponding to grade (3+/4+), was detected in 40/90 (44%) patients. Six weeks after the CRT implantation, the distribution of the FMR grades in the subset of patients who presented with at least FMR(2+) at baseline was as follows: FMR(1+) 15/90 (17%) patients, FMR(2+) 21/90 (23%) patients, FMR(3+) 23/90 (26%) patients, and FMR(4+) 7/90 (8%) patients. The patients with baseline FMR ≥ (2+) were divided into two groups: Group A with FMRI (n = 30) and Group B without FMRI (n = 36).

Baseline demographic and clinical characteristics of the study groups are presented in Table 1. The groups did not differ significantly in terms of age, gender, aetiology (ischaemic vs. non-ischaemic), NYHA class, and medication.

Baseline electrocardiographic and echocardiographic characteristics of the study groups are presented in Table 2. The groups did not differ significantly in terms of QRS width. Furthermore, no significant differences in LV volumes, LVEF, and site of the latest activation were found. The only significant differences pertained to LVEDD and one of dyssynchrony measures — IVD: patients from Group A were characterised by significantly smaller LVEDD (p = 0.041) and significantly longer IVD (p = 0.016) than individuals from Group B (Table 2).

Difference in the presence of contractile reserve between groups

The incidence of contractile reserve in the study groups is summarised in Table 3. Patients from Group A showed the LDSE evidence for contractile reserve significantly more often than those from Group B: contractile reserve, defined as a relative improvement in LVEF of more than 20% ($\uparrow\Delta$LVEF > 20%), was detected significantly more often in Group A than in Group B (90% vs. 69%, p < 0.05), and the difference in the incidence of the relative improvement in WMSI more than 20% ($\downarrow\Delta$WMSI > 20%) was at the threshold of statistical significance (Table 3).

Predictors of FMRI six weeks after CRT implantation

The LDSE evidence for contractility improvement in more than three segments (OR = 5.7, 95% CI 1.81–17.97, p = 0.005, sensitivity 65.5%, specificity 72.2%, AUC = 0.727) and baseline LVEDD ≤ 74 mm (OR = 2.09, 95% CI 0.75–5.78, p < 0.05, sensitivity 80.0%, specificity 47.2%, AUC = 0.632) were identified as independent predictors of FMRI on Cox regression multivariate analysis.

Impact of FMRI on the incidence of LV reverse remodelling

The presence of FMRI six weeks after CRT implantation was associated with significantly greater reduction of LVESV

Table 1. Comparison of baseline clinical characteristics between groups

Feature	Group A; with FMRI (n = 30)	Group B; without FMRI (n = 36)	A vs. B
Age [years]			$p^a = 0.263$
Mean ± SD	62.1 ± 8.3	64.8 ± 10.7	
Median	62.5	64	
Min ÷ max	40 ÷ 78	31 ÷ 82	
Male gender:	19 (63.3%)	30 (83.3%)	$p^b = 0.064$
NYHA functional class:			$p^b = 0.509$
Class II	6 (20.7%)	3 (9.1%)	
Class III	22 (75.9%)	27 (81.8%)	
Class IV	1 (3.4%)	3 (9.1%)	
Aetiology (non-ischaemic)	14 (46.7%)	20 (55.6%)	$p^b = 0.637$
Previous myocardial infarction	16 (53.3%)	19 (52.8%)	$p^b = 0.839$
Hypertension	14 (46.7%)	24 (66.7%)	$p^b = 0.165$
Diabetes	8 (26.7%)	12 (33.3%)	$p^b = 0.751$
Dyslipidaemia	16 (55.2%)	25 (71.4%)	$p^b = 0.277$
Atrial fibrillation	2 (7.4%)	4 (12.9%)	$p^c = 0.404$
Medications:			
Beta-blockers	29 (96.7%)	35 (97.2%)	$p^c = 1.000$
ACE-I	27 (90%)	29 (80.6%)	$P^c = 0.327$
ARB	2 (6.7%)	4 (11.1%)	$p^c = 0.681$
Spironolactone	19 (63.3%)	30 (83.3%)	$p^b = 0.117$
Diuretics	25 (83.3%)	33 (91.7%)	$p^c = 0.452$
Digoxin	6 (20.0%)	5 (13.9%)	$p^b = 0.740$

[a]Unpaired Student's t-test; [b]Pearson χ^2 test; [c]Fisher's exact test; FMRI — functional mitral regurgitation improvement; SD — standard deviation; NYHA — New York Heart Association; ACE-I — angiotensin converting enzyme inhibitors; ARB — angiotensin receptors blockers

(–38 ± 27 mL in Group A vs. –12 ± 36 mL in Group B, p = 0.002) and greater increase in LVEF (+10.1 ± 8.5% in Group A vs. +2.3 ± 5.5% in Group B, p < 0.001; Table 4). The incidence of the LV reverse remodelling defined as the reduction of the LVESV by at least 15% (↓ ΔLVESV ≥ 15%) was significantly higher in Group A than in Group B (62.8% vs. 37.2%, p < 0.001). The chance to improve ↓ ΔLVESV ≥ 15% after six weeks of CRT in Group A (with FMRI) was 11-fold higher than in Group B (without FMRI). Also significantly higher incidence of LV reverse remodelling defined as the increase of the LVEF by at least 15% (↑ ΔLVEF ≥ 15%) was demonstrated in Group A compared to Group B (76.6% vs. 23.5%, p < 0.01). The chance to improve ↑ ΔLVEF ≥ 15% after six weeks of CRT in Group A was six-fold higher than in Group B.

DISCUSSION

Incidence of FMRI in patients undergoing CRT

Functional mitral regurgitation is present in a large percentage of the population of patients eligible for CRT. Effective CRT immediately reduces the transmitral regurgitant volume at rest in about 40% of patients [2]. The FMRI observed in a further 10–20% of the patients is probably related to the LV reverse remodelling and changes in the geometry of mitral apparatus [2, 9]. It is believed that this latter effect appears at mid- and long-term follow-up (months) after CRT implantation [2, 6, 9].

Di Biase et al. [15] showed that 86% of patients included in a prospective registry (n = 398) presented with FMR at the time of CRT implantation; 35% of the whole population was diagnosed with severe FMR(3+/4+). After 12 months of CRT, FMRI by at least one grade was documented in 46% of these patients, relatively more often in individuals who presented with severe FMR(3+/4+) at baseline (63%) [15]. In turn, Cabrera-Bueno et al. [16] recognised significant FMR (effective regurgitant orifice area [EROA] ≥ 0.2 cm^2) in 43% of the 76 patients qualified to CRT; in 34% of them, FMR was no longer significant six months after the CRT implantation. To the best of our knowledge, our study was the first to assess the incidence of FMRI six weeks after CRT implantation, i.e. after a short follow-up. The incidence of FMR at baseline was generally similar to that documented in previous studies: 63% of our patients presented with at least FMR(2+), and 44% were diagnosed with severe FMR(3+/4+). Six weeks

Table 2. Comparison of baseline electrocardiographic and echocardiographic parameters between groups (mean ± standard deviation)

Parameter	Group A; with FMRI (n = 30)	Group B; without FMRI (n = 36)	A vs. B
QRS duration [ms]	168 ± 20	160 ± 23	$p^a = 0.139$
LVEDV [mL]	217 ± 30	263 ± 125	$p^a = 0.074$
LVDD [mm]	69 ± 8	74 ± 11	$p^a = 0.041$
LVESV [mL]	158 ± 30	199 ± 107	$p^a = 0.055$
LVSD [mm]	60 ± 8	62 ± 12	$p^a = 0.309$
LVEF [%]	26.5 ± 6.0	24.9 ± 6.0	$p^a = 0.294$
Left atrium [mm]	46.1 ± 10.1	46.4 ± 7.4	$p^a = 0.925$
Left atrium area [cm^2]	26.5 ± 8.3	27.8 ± 8.2	$p^a = 0.554$
Interventricular delay [ms]	53 ± 30	33 ± 40	$p^a = 0.016$
Intraventricular dyssynchrony max. (ms)	120 ± 73	96 ± 95	$p^a = 0.267$
Inter- and Intraventricular dyssynchrony (ms)	140 ± 67	119 ± 46	$p^a = 0.202$
DFT/R-R (%)	44.6 ± 10.7	44.0 ± 12.0	$p^a = 0.856$
Site of latest activation:			$p^b = 0.116$
Inferolateral wall	15 (51.7%)	11 (33.3%)	
Anterior wall	6 (20.7%)	15 (45.5%)	
Inferior wall	8 (27.6%)	7 (21.2%)	

LVEDV — left ventricular end-diastolic volume; LVEDD — left ventricular end-diastolic dimension; LVESV — left ventricular end-systolic volume; LVESD — left ventricular end-systolic dimension; LVEF — left ventricular ejection fraction; DFT/R-R — left ventricular diastolic filling time to cardiac cycle length ratio

Table 3. Comparison of the incidence of preserved contractile reserve between the two groups

Preserved contractile reserve in LDSE parameter	Group A; with FMRI; 6 weeks of CRT (n = 30)	Group B; without FMRI; 6 weeks of CRT (n = 36)	A vs. B
Δ LVEF > 20%	27 (90%)	25 (69.4%)	$p^c = 0.039$
Δ WMSI > 20%	26 (86.7%)	24 (66.7%)	$p^c = 0.053$

[c]Fisher's exact test; LDSE — low-dose dobutamine stress-echo; FMRI — functional mitral regurgitation improvement; CRT — cardiac resynchronisation therapy; LVEF — left ventricular ejection fraction; WMSI — wall motion score index

Table 4. Comparison of the changes of the analysed parameters in both groups six weeks after cardiac resynchronisation therapy implantation

Parameter change	Group A; with FMRI (n = 30)	Group B; without FMRI (n = 36)	A vs. B
$\Delta QRS = QRS_{6w} - QRS_0$	–22 ± 23	–15 ± 34	$p^a = 0.371$
$\Delta LVEDV = LVEDV_{6w} - LVEDV_0$	–29 ± 34	–12 ± 39	$p^a = 0.070$
$\Delta LVEDD = LVEDD_{6w} - LVEDD_0$	–4 ± 5	–3 ± 5	$p^a = 0.718$
$\Delta LVESV = LVESV_{6w} - LVESV_0$	–38 ± 27	–12 ± 36	$p^a = 0.002$
$\Delta LVESD = LVESD_{6w} - LVESD_0$	–5 ± 6	–3 ± 5	$p^a = 0.221$
$\Delta LVEF = LVEF_{6W} - LVEF_0$	+10.1 ± 8.5	+2.3 ± 5.5	$p^a < 0.001$
$\Delta LA\ area = LA\ area_{6W} - LA\ area_0$	–2.8 ± 3.5	–0.8 ± 5.7	$p^a = 0.097$
$\Delta IVD = IVD_{6W} - IVD_0$	–32.1 ± 32.2	–17.3 ± 35.4	$p^a = 0.100$
$\Delta DFT/R\text{-}R\ (\%) = DFT/R\text{-}R_{6W} - DFT/R\text{-}R_0$	+6.5 ± 11.6	+2.0 ± 14.6	$p^a = 0.175$

[a]Unpaired Student's t-test; QRS — QRS duration; 6W — six weeks; 0 — baseline; LVEDV — left ventricular end-diastolic volume; LVEDD — left ventricular end-diastolic dimension; LVESV — left ventricular end-systolic volume; LVESD — left ventricular end-systolic dimension; LVEF — left ventricular ejection fraction; LA — left atrium; IVD — interventricular delay; DFT/R-R — left ventricular diastolic filling time to cardiac cycle length ratio

after the CRT implantation, FMRI by at least one grade was documented in one-third of the patients. Our observation suggests that the improvement of FMR associated with the LV reverse remodelling may occur much earlier than a few months after the CRT implantation.

FMRI and the LV reverse remodelling after CRT implantation

Response to CRT may be modulated by the presence of FMR prior to the implantation and its persistence despite the treatment. The CARE-HF study revealed that the 'non-responders' presented with significant FMR more often than the individuals who responded to CTR [7]. In turn, Liang et al. [17] found that an improvement in pre-existing FMR contributed to LV reverse remodelling during a three-month follow-up after CRT implantation. The incidence of the reverse remodelling, expressed as LVEF and forward stroke volume improvement, turned out to be highest in patients who showed reduction of total FMR, intermediate in individuals with mild FMR or lack thereof at the baseline, and lowest in persons without improvement in total FMR after thee months of post-CRT follow-up [17].

Despite a shorter observation period, our findings are consistent with the abovementioned data. The patients who presented with FMRI six weeks after CRT implantation showed evidence for LV reverse remodelling significantly more often than those without improvement of FMR. However, we did not document corresponding changes in the analysed clinical parameters, i.e. at least one class decrease in the NYHA classification. This observation is not surprising for at least two reasons: probably too short follow-up period and the evidence for rather poor correlation between clinical and echocardiographic markers of post-CTR improvement [6]. Previous studies showed that clinical response to CTR might be observed despite the lack of volumetric changes and vice versa [18]. Yu et al. [19] demonstrated that the direction and magnitude of the LV reverse remodelling correlate with survival, and showed that one-year mortality after CRT is predicted by echocardiographic parameters rather than by clinical indices.

Our results suggest that the LV reverse remodelling (related with the improvement of FMR and probably constituting one of the mechanisms for this improvement) occurs much earlier than previously thought and despite the lack of clinical improvement.

Dyssynchrony and FMRI after CRT implantation

Agricola et al. [8] demonstrated that the severity of FMR is mainly associated with the indices of mitral apparatus deformation; also the regional tissue Doppler-derived dyssynchrony index proved to be an independent determinant of EROA in their study, but only in patients with non-ischemic LV dysfunction. In their review paper, Smiseth et al. [20] emphasised the fact that the clinical value of many proposed echocardiographic parameters of the LV dyssynchrony is poorly proven. Many of the proposed echocardiographic indices of dyssynchrony proved to be inaccurate in a clinical setting due to their poor reproducibility and high intra-/interobserver variability [18].

Inter-ventricular delay turned out to be the only baseline marker of dyssynchrony that distinguished between our patients showing FMRI six weeks after CRT implantation and those who did not. Stockburger et al. [21] identified LV pre-ejection interval and interventricular mechanical delay (an equivalent of our IVD) as the predictors of response to CRT, namely the LV reverse remodelling. Although the underlying mechanisms are not clear, particularly in the case of FMR, either the LV pre-ejection interval or IVD prolongation seem to be correlated with the degree of left bundle branch block — the main determinant of primary electrical dyssynchrony. Ypenburg et al. [2] used echocardiographic assessment of the baseline latest activation sites to explain detailed mechanisms of early (one-day) and late (six-month) FMRI after CRT implantation. The LV dyssynchrony with involvement of the posterior papillary muscle resulted in immediate FMR changes, whereas the LV dyssynchrony in the lateral wall determined late response to the resynchronisation therapy [2, 10]. In our six-week observation we did not find any relationship between the site of latest activation and FMRI; this indicates that mechanisms responsible for improvement are more complex.

Inotropic contractile reserve and FMRI after CRT implantation

Myocardial viability and contractile reserve belong to the determinants of CRT effectiveness in both ischaemic and non-ischaemic cardiomyopathy [11–14]. Lim et al. [11] used LDSE to assess contractile reserve, and demonstrated that contractile reserve preserved in the paced LV region correlates with an acute haemodynamic response and the LV reverse remodelling six months after CRT. However, these authors did not analyse the relationship between contractile reserve and FMRI in response to CRT.

To the best of our knowledge, the impact of preserved contractile reserve on FMRI after CRT implantation has not been studied thus far. Our study revealed that the patients who showed improvement of FMR six weeks after CRT implantation more often presented with the LDSE evidence for contractile reserve at baseline. Moreover, we showed that post-CRT improvement of FMR might be expected only if the area of contractile reserve documented on baseline LDSE was larger than three segments of the LV. The increase in the contractility in at least four segments turned out to be an independent predictor of FMRI six weeks after CRT implantation. It should be emphasised that this relationship has been demonstrated for at least four of any viable segments because it does not analyse the relationship between LV electrode location and the location of the viable area. This may suggest

a dominant influence of improvement of global rather than local remodelling on FMRI after CRT implantation.

Our study was probably the first to evaluate the relationship between baseline contractile reserve and post-CRT improvement of FMR. However, a similar study conducted by Senechal et al. [22] should be mentioned; the authors analysed the contractile reserve area as a predictor of response to CRT. They studied the relationship between the LDSE evidence for contractile reserve and FMR prior to CRT implantation and acute response to the resynchronisation therapy (defined as a relative increase in LV stroke volume more than 15%). The average number of viable segments in responders and non-responders was 5.8 and 3.9, respectively, and 84% of the patients with acute response showed FMRI [22]. The co-existence of functional mitral regurgitation and viability in the region of the pacing lead turned out to be the most accurate predictor of acute response to CRT [22]. In our study we did not analyse the location of viable segments, nevertheless there was a relationship between the size of the contractile reserve area and the occurrence of FMRI. All these findings suggest that the response to CRT can be predicted on the basis of concomitantly determined: contractile reserve, incidence of FMR, and dynamics of the latter parameter.

Volumetric limitations for FMRI after CRT implantation

We showed that the post-CRT improvement in FMR was less likely in patients who presented with greater degree of LV dilatation. LVEDD less than 74 mm turned out to be the independent predictor of FMRI. Diaz-Infante et al. [23] also demonstrated a similar size-dependent limit for response to CRT. They identified ischaemic heart disease, severe FMR, and LV end-diastolic diameter ≥ 75 mm as independent predictors of lack of response to CRT. Similarly, Stellbrink et al. [24] showed that the non-responders presented with significantly higher baseline LVEDV than the patients who responded to CRT.

Both our findings and the results of previous studies suggest that CRT may be insufficient to overcome poor natural history of systolic heart failure but may slow down its progression. The effectiveness of all available therapeutic methods is limited, and critically enlarged LV may trigger the previously mentioned vicious circle of self-perpetuating LV dilatation and functional mitral regurgitation [25].

Limitations of the study

We estimated the severity of FMR semi-quantitatively, by currently recommended integrative approach. However, according to American Society of Echocardiography and European Association of Echocardiography (now the European Association of Cardiovascular Imaging) the severity of mitral regurgitation should be determined on the basis of multiple parameters, in order to minimise the bias inherent to each individual method, mainly due to their well-known poor reproducibility and high intra- and interobserver variability. Another potential limitation of our study stems from the fact that we did not evaluate the compatibility of the location of segments showing preserved contractile reserve with the site of LV pacing lead. Despite this we have shown the relationship between the size of contractile reserve area and FMRI.

CONCLUSIONS

1. Preserved contractile reserve and lesser degree of LV dilation were predictive factors of short-term FMRI after CRT implantation.
2. FMRI was associated with higher incidence of the LV reverse remodelling early — already in the six weeks after CRT implantation.

Conflict of interest: *None declared*

References

1. Breithardt OA, Sinha AM, Schwammenthal E et al. Acute effect of cardiac resynchronization therapy on functional mitral regurgitation in advanced systolic heart failure. J Am Coll Cardiol, 2003; 41: 765–770. doi: 10.1016/S0735-1097(02)02937-6.
2. Ypenburg C, Lancellotti P, Tops LF et al. Mechanism of improvement in mitral regurgitation after cardiac resynchronization therapy. Eur Heart J, 2008; 29: 757–765. doi: 10.1093/eurheartj/ehn063.
3. Grigioni F, Enriquez-Sarano M, Zehr KJ et al. Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative doppler assessment. Circulation, 2001; 103: 1759–1764. doi: 10.1161/01.CIR.103.1759.
4. Otsuji Y, Handschumacher MD, Schwammenthal E et al. Insights from three-dimensional echocardiography into the mechanism of functional mitral regurgitation: direct in vivo demonstration of altered leaflet tethering geometry. Circulation, 1997; 96: 1999–2008. doi: 10.1161/01.CIR.96.6.1999.
5. Trichon BH, Felker GM, Shaw LK et al. Relation of frequency and severity of mitral regurgitation to survival among patients with left ventricular systolic dysfunction and heart failure. Am J Cardiol, 2003; 91: 538–543. doi: 10.1016/S0002-9149(02)03301-5.
6. St. John Sutton MG, Plappert T, Abraham WT et al. Multicenter InSync Randomized Clinical Evaluation (MIRACLE) Study Group. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. Circulation, 2003; 107: 1985–1990. doi: 10.1161/01.CIR.0000065226.24159.E9.
7. Cleland JG, Daubert JC, Erdmann E et al.; for the Cardiac Resynchronization-Heart Failure CARE-HF Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med, 2005; 352: 1539–1549. doi: 10.1056/NEJMoa050496.
8. Agricola E, Oppizzi M, Galderisi M et al. Role of regional mechanical dyssynchrony as a determinant of functional mitral regurgitation in patients with left ventricular systolic dysfunction. Heart, 2006; 92: 1390–1395. doi: 10.1136/hrt.2005.082115.
9. Madaric J, Vanderheyden M, Van Laethem C et al. Early and late effect of cardiac resynchronization therapy on exercise-induced mitral regurgitation: relationship with left ventricular dyssynchrony, remodelling and cardiopulmonary performance. Eur Heart J, 2007; 28: 2134–2141. doi: 10.1093/eurheartj/ehm126.
10. Kanzaki H, Bazaz R, Schwartzman D et al. A mechanism for immediate reduction in mitral regurgitation after cardiac resynchronization therapy. Insight from mechanical activation strain mapping. J Am Coll Cardiol, 2004; 44: 1619–1625. doi: 10.1061/j.jacc.2004.07.036.

11. Lim P, Bars C, Mitchell-Heggs L et al. Importance of contractile reserve for CRT. Europace, 2007; 9: 739–743. doi: 10.1093/europace/eum117.
12. Ramahi TM, Longo MD, Cadariu AR et al. Dobutamine-induced augmentation of left ventricular ejection fraction predicts survival of heart failure patients with severe non-ischemic cardiomyopathy. Eur Heart J, 2001: 22: 849–856. doi: 10.1053/euhj.2001.2654.
13. Gasparini M, Muto C, Iacopino S et al. Low-dose dobutamine test associated with interventricular dyssynchrony: a useful tool to identify cardiac resynchronization therapy responders: data from the LODO-CRT phase 2 study. Am Heart J, 2012; 163: 422–429. doi: 10.1016/j.ahj.2011.11.015.
14. Mizia-Stec K, Wita K, Mizia A et al. Preserved contractile reserve in a dobutamine test for the prediction of a response to resynchronization therapy in ischaemic and non-ischaemic cardiomyopathy: a multicenter ViaCRT study. Letters to the Editor. Int J Cardiol, 2014; 172: 476–477. doi: 10.1016/j.ijcard.2013.12.204.
15. Di Biase L, Auricchio A, Mohanty P et al. Impact of cardiac resynchronization therapy on the severity of mitral regurgitation. Europace, 2011; 13: 829–838. doi: 10.1093/europace/eur047.
16. Cabrera-Bueno F, Molina-Mora MJ, Alzueta J et al. Persistence of secondary mitral regurgitation and response to cardiac resynchronization therapy. Eur J Echocardiogr, 2010; 11: 131–137. doi: 10.1093/ejechocard/jep184.
17. Liang YJ, Zhang Q, Fung JW et al. Impact of reduction in early- and late-systolic functional mitral regurgitation on reverse remodelling after cardiac resynchronization therapy. Eur Heart J, 2010; 31: 2359–2368. doi: 10.1093/eurheartj/ehq212.
18. Chung ES, Leon AR, Tavazzi L et al. Results of the predictors of response to CRT (PROSPECT) Trial. Circulation, 2008; 117: 2608–2616. doi: 10.1161/CIRCULATIONAHA.107.743120.
19. Yu CM, Bleeker GB, Fung JW et al. Left ventricular reverse remodeling but not clinical improvement predicts long-term survival after cardiac resynchronization therapy. Circulation, 2005; 112: 1580–1586. doi: 10.1161/CIRCULATIONAHA.105.538272.
20. Smiseth OA, Russell K, Skulstad H. The role of echocardiography in quantification of left ventricular dyssynchrony: state of the art and future direction. Eur Heart J Cardiovasc Imaging, 2012; 13: 61–68. doi: 10.1093/ejechocard/jer243.
21. 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. doi: 10.1093/europace/eum269.
22. Sénéchal M, Lancellotti P, Garceau P et al. Usefulness and limitation of dobutamine stress echocardiography to predict acute response to cardiac resynchronization therapy. Echocardiography, 2010; 27: 50–57. doi: 10.1111/j.1540-8175.2009.00962.x.
23. Diaz-Infante E, Mont L, Leal J et al. SCARS Investigators. Predictors of lack of response to resynchronization therapy. Am J Cardiol, 2005; 95: 1436–1440. doi: 10.1016/j.amjcard.2005.02.009.
24. Stellbrink C, Breithardt OA, Franke A et al. Impact of cardiac resynchronization therapy using hemodynamically optimized pacing on left ventricular remodeling in patients with congestive heart failure and ventricular conduction disturbances. J Am Coll Cardiol, 2001; 38: 1957–1965. doi: 10.1016/S0735-1097(01)01637-0.
25. Brzezińska B, Łoboz-Grudzień K, Sokalski L. Patterns of post-MI left ventricular volume changes: clinical implications. Kardiol Pol, 2007; 65: 1190–1198.

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Czynniki prognostyczne poprawy czynnościowej niedomykalności zastawki mitralnej w krótkoterminowej obserwacji po wszczepieniu układu resynchronizującego

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Streszczenie

Wstęp i cel: Celem pracy była ocena wartości prognostycznej rezerwy kurczliwości mięśnia sercowego w przewidywaniu poprawy czynnościowej niedomykalności zastawki mitralnej (FMR) po wszczepieniu układu resynchronizującego (CRT), a także zdefiniowanie innych predyktorów poprawy FMR (FMRI) oraz wpływu FMRI na wystąpienie odwrotnego remodelingu lewej komory.

Metody i wyniki: Badanie jest subanalizą wieloośrodkowego programu klinicznego *The Myocardial Viability in Cardiac Resynchronization Therapy* (ViaCRT). Spośród 90 pacjentów, u których badanie echokardiograficzne wykonano w dniu poprzedzającym wszczepienie układu CRT, a następnie po 6 tygodniach, do analizy włączono 66 osób z FMR co najmniej 2 stopnia (FMR[2+]) w 4-stopniowej skali czynnościowej niedomykalności zastawki mitralnej (śr. wiek 64 ± 10, śr. LVEF 25,7 ± 6%, etiologia niedokrwienna 48%). FMRI zdefiniowano jako redukcję stopnia ciężkości FMR o co najmniej 1 stopień. Pacjenci zostali podzieleni na dwie grupy: grupa A — z FMRI (n = 30) oraz grupa B — bez FMRI (n = 36). Rezerwę kurczliwości oceniano za pomocą echokardiograficznej próby dobutaminowej niskiej dawki wykonanej w dobie przed wszczepieniem CRT i została ona zdefiniowana jako względna poprawa LVEF powyżej 20% oraz poprawa kurczliwości segmentalnej. Odwrotny remodeling zdefiniowano jako względną redukcję końcowoskurczowej objętości lewej komory (LVESV) o co najmniej 15%. Wieloczynnikowa analiza regresji Coxa ujawniła następujące predyktory FMRI: zachowana rezerwa kurczliwości w więcej niż trzech segmentach komory z ilorazem szans (OR) = 5,7 (95% CI 1,81–17,97; p = 0,005; czułość 65,5%; specyficzność 72.2%; AUC = 0,727) oraz końcoworozkurczowy wymiar lewej komory ≤ 74 mm z OR = 2,09 (95% CI 0,75–5,78; p < 0,05; czułość 80,0%; specyficzność 47,2%; AUC = 0,632). FMRI wiązała się z większym stopniem redukcji LVESV (p = 0,002), większą poprawą LVEF (p < 0,001) oraz częstszym występowaniem odwrotnego remodelingu (p < 0,001).

Wnioski: Zachowana rezerwa kurczliwości i mniejszy stopień powiększenia lewej komory były czynnikami prognostycznymi wczesnej poprawy FMR po wszczepieniu CRT. Poprawa FMR wiązała się z częstszym występowaniem odwrotnego remodelingu lewej komory wcześnie, już w 6. tygodniu po wszczepieniu CRT.

Słowa kluczowe: terapia resynchronizująca, czynnościowa niedomykalność zastawki mitralnej, echokardiograficzna próba dobutaminowa, rezerwa kurczliwości mięśnia sercowego, odwrotny remodeling w niewydolności serca

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