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Echocardiography-based qualification and response assessment to cardiac resynchronisation therapy in patients with chronic heart failure. The matrix metalloproteinase-9 substudy

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Abstract

Background: The concept of cardiac resynchronisation therapy (CRT) is based on biventricular pacing in symptomatic, chronic heart failure (HF) patients with systolic left ventricular (LV) dysfunction and QRS ≥ 120 ms. The response to CRT is determined by clinical and echocardiographic parameters. The change of biochemical status (e.g. natriuretic peptides or metalloproteinase levels) caused by CRT is not well explored.

Aim: To analyse the clinical and haemodynamic changes caused by CRT in relation to patients' biochemical status and to assess factors determining a favourable response to CRT.

Methods: Fifty patients with chronic systolic HF (NYHA IV: two patients), wide QRS complex (160 ± 31 ms) and reduced LV ejection fraction (26 ± 5.8%) under optimal pharmacotherapy, who underwent CRT, were enrolled. Data on NT-proBNP and C-reactive protein serum levels, as well as standard echocardiography with tissue Doppler measurements, were collected before CRT and after six months of pacing. The levels of matrix metalloproteinase-9 (MMP-9) were assessed in a subgroup of 18 patients. Patients were regarded as responders if LV end-systolic volume decreased by 10% compared to baseline.

Results: Thirty five (70%) patients responded favourably to CRT. Cardiac resynchronisation therapy resulted in an improvement of max. ventilatory oxygen uptake (12.9 ± 3.8 *vs* 16.6 ± 4.7 mL/kg/min; $p < 0.05$), a of NT-proBNP decrease (2,579 ± 2,598 *vs* 1,339 ± 1,088 pg/mL, $p < 0.05$), and decrease of atrio-, inter- and intra-LV dyssynchrony. A greater baseline dyssynchrony was observed in responders. A decrease of MMP-9 level following CRT was observed in 12 (67%) patients. Significant MMP-9 decrease was observed only in the subgroup of ischaemic HF patients (26,100 ± 7,624 pg/mL *vs* 23,360 ± 6,258 pg/mL; $p = 0.03$). In patients with MMP-9 decrease during CRT, a lower C-reactive protein concentration at baseline was observed (2.12 ± 1.6 *vs* 4.7 ± 4.1 mg/L). The reduction in LV end-diastolic diameter correlated with the changes in MMP-9 level ($r = 51$; $p = 0.03$). Baseline left atrial end-diastolic diameter measured in parasternal long-axis view ≤ 46 mm had a sensitivity of 83% and a specificity of 67% in predicting MMP-9 decrease (AUC 0.83; 95% CI 0.59–0.96).

Conclusions: The CRT induces favourable myocardial remodelling, resulting in NT-proBNP level decrease, improvement of regional and global biventricular function, and MMP-9 level reduction, in ischaemic HF patients. The changes of MMP-9 level may be predicted by baseline left atrial end-diastolic diameter and correlate with LV end-diastolic diameter change during CRT.

Key words: cardiac resynchronisation therapy, metalloproteinase, heart failure, echocardiography

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INTRODUCTION

The assessment of ventricular mechanical dyssynchrony is the key to identify patients with chronic heart failure (HF) who could benefit from cardiac resynchronisation therapy (CRT). Nowadays, the recommended method for patient selection is a 12-lead surface ECG, where QRS width ≥ 120 ms is a recognised marker of mechanical ventricular dyssynchrony. The CRT has been documented to be beneficial in terms of both clinical status and reverse left ventricular (LV) remodelling. Standard criteria recommended by the European Society of Cardiology [1] and American Heart Association [2] are based on the following clinical and electrocardiographic aspects: (1) New York Heart Association (NYHA) class III–IV, (2) prolonged QRS duration ≥ 120 ms, (3) optimal pharmacotherapy, (4) decreased LV ejection fraction (LVEF), ≤ 35% [1, 2] and (5) sinus rhythm [1]. However, about 30% of patients with chronic HF selected according to current criteria do not respond favourably to CRT. Thus, it seems that duration of QRS complex is not a sufficient parameter and some additional measurements of dyssynchrony are needed. In this regard, tissue Doppler imaging (TDI) has been proposed.

Theoretically, CRT should lead to LV stroke volume increase and improve exercise tolerance of chronic HF patients, and thus haemodynamic and clinical response. Resynchronisation was mentioned as a therapy that probably reduced the symptoms of HF (level of evidence B) for the first time in 2001 [3]. The first report on percutaneous transvenous LV lead implantation was published in 1998 [4]. During the last decade, there has been dynamic progress in CRT implantation techniques, e.g. using dual site LV stimulation [5]. The CRT is recommended for an increasing number of targets: reducing symptoms, hospitalisations and mortality [6]. On the other hand, CRT has been reported to act on the basic, biochemical level to reduce the immune activation frequently noted in chronic HF patients [7].

The aim of this study was to analyse the clinical and haemodynamic changes under CRT in relation to patients' biochemical status and to assess the factors determining a favourable response to CRT.

METHODS

The study group comprised 50 patients with chronic systolic HF (NYHA IV: two patients), wide QRS complex (160 ± 31 ms) and LVEF (26 ± 5.8%) under optimal pharmacotherapy, who underwent CRT. Optimal pharmacotherapy included the use of beta-blockers (all patients), angiotensin converting enzyme inhibitors and/or angiotensin II AT1 receptors antagonists (all patients) — at least 90 days prior to CRT. The baseline demographic and clinical data of patients are presented in Table 1.

The research protocol was approved by the local ethics committee. The patients gave informed written consent to undergo standard diagnostic and therapeutic procedures, including CRT implantation and echocardiographic studies.

Table 1. Baseline characteristics of the study group

Age [years]	59 ± 11
Men	41 (82%)
Ischaemic aetiology:	21 (42%)
Scar within left ventricular myocardium	9 (18%)
NYHA IV class	2 (4%)
Co-morbidities:	
Diabetes	20 (40%)
Arterial hypertension	18 (36%)
Hypercholesterolaemia	15 (30%)
Smokers	21 (42%)

Patient enrolment

The study group consisted of patients fulfilling recommended criteria [1]: optimal pharmacotherapy, NYHA class III or IV, QRS duration ≥ 120 ms and LVEF (assessed using Simpson's biplane method) ≥ 35% and optimal revascularisation, evidenced by coronary angiogram within two years before CRT, without new symptoms of myocardial ischaemia. Otherwise, coronary angiography and adequate treatment were performed and CRT delayed. Patients with potentially reversible reasons of systolic HF were not enrolled in the study.

The patients' data were collected at baseline before CRT implementation and at a six month follow-up visit. Additionally, after device implantation, at discharge, optimisation of resynchronisation function (interventricular and atrio-ventricular delays) under echocardiographic guidance was performed. Patients were regarded as responders if LV end-systolic volume (LVESV) decreased by 10% compared to baseline.

Biochemical assessment

Electrochemiluminescence quantitative (Roche) method was used to determine the NT-proBNP serum level, with the reference ≤ 125 pg/mL. The RayBio® Human Matrix metalloproteinase-9 (MMP-9) ELISA (Enzyme-Linked Immunosorbent Assay) kit was used for the quantitative measurement of human MMP-9 forms in serum. This assay employs an antibody specific for human MMP-9. Among routine laboratory measurements, C-reactive protein (CRP) serum level was determined.

Exercise tolerance testing

To assess exercise tolerance, ventilatory oxygen uptake (VO_2) and 6-minute walk test (6-MWT) were performed. The VO_2 test was performed on a treadmill VMAX 229D (SensorMedics, Viasys Healthcare Inc., Conshohocken, PA, USA) using modified Bruce protocol, with increasing workload every three minutes.

Table 2. The impact of cardiac resynchronisation therapy (CRT) on standard CRT criteria and selected biochemical parameters

	Baseline	Six months of follow-up	P
NYHA class	2.8 ± 0.4	2 ± 0.6	< 0.05
QRS [ms]	160 ± 31	153 ± 36	NS
6MWT [m]	304 ± 98	370 ± 88	< 0.05
VO_2 [mL/kg/min]	12.9 ± 3.8	16.6 ± 4.7	< 0.05
LVEF biplane [%]	26 ± 5.8	35 ± 8.6	< 0.05
MMP-9 [pg/mL] (n = 18)	27,422 ± 8,068	25,994 ± 7,091	NS
NT-proBNP [pg/mL]	2,579 ± 2,598	1,339 ± 1,088	< 0.05

NYHA — New York Heart Association; 6MWT — 6-minute walk test; VO_2 — maximum ventilatory oxygen uptake; LVEF — left ventricular ejection fraction; MMP-9 — matrix metalloproteinase-9; NT-proBNP — N-terminal pro-brain natriuretic peptide type B

Echocardiographic study

Echocardiographic study was performed using Vivid 5 system (GE, Horten, Norway) with 2.5 MHz probe and archived in a DICOM format for further off-line analysis on an EchoPac 6.4.2 workstation (GE Vingmed Ultrasound) [8]. The images of one cardiac cycle obtained using parasternal long-axis (Lax) view, and apical four-, three- and two-chamber views (A4C, A3C and A2C) were stored in two applications: conventional grey scale and TDI. Interventricular synchrony was assessed based on conventional Doppler pulse-wave signal as the time difference between the right ventricular (RV) and LV pre-ejection periods.

The ratio of diastolic filling time and cardiac cycle duration below 0.4 (< 40%) was perceived as the atrio-ventricular dyssynchrony. Intraventricular dyssynchrony was assessed based on velocity (time to onset and time to peak of systolic velocity) and strain (time to peak strain) profiles retrieved from TDI data. The onset of QRS complex was used as the reference for all temporal measurements. Six LV walls and free RV wall at basal and medial level were analysed.

Statistical analysis

Continuous parameters are expressed as mean ± SD. Grouped data were tested for normal (Gaussian) distribution and equality of SD (Kolmogorov-Smirnov) and compared using a two-tailed t-test. Probability values of $p < 0.05$ were considered statistically significant. Pearson's coefficient (r) was used to assess correlations. Receiver operating characteristics (ROC) analysis, followed by area under curve (AUC) analysis, were performed to determine the specificity and sensitivity of selected parameters for differentiation between responder and non-responder groups and MMP-9 change groups. For parameters presenting with AUC > 0.7, the cut-off value was assessed. Analyses were performed using Statistica software packages (version 6.1, StatSoft Inc., Tulsa, OK, USA).

RESULTS

Response to cardiac resynchronisation therapy

In the whole study group, CRT was beneficial in regard to the majority of parameters which are CRT standard criteria (Table 2). All patients survived six months of follow-up. The haemodynamic response rate was 35 (70%) patients.

Reduced LV and left atrial diameters and volumes, as well as diminished mitral and tricuspid regurgitations were observed following the CRT. The CRT influenced right heart chambers to a lesser degree, and did not change the LV end-diastolic pressure (E/E') (Table 3).

Although the serum level of NT-proBNP decreased significantly following CRT implementation (Table 2, Fig. 1A), there was only a trend towards the decrease of MMP-9 concentration in the whole group of patients undergoing CRT (Table 2, Fig. 1B).

Biventricular pacing resulted in shortening of inter-ventricular, atrio-ventricular and intra-LV dyssynchrony as measured by time to onset or time to peak of systolic myocardial velocity. The detailed results are presented in Table 4.

Matrix metalloproteinase-9

The MMP-9 measurements were performed in the last 18 consecutive patients enrolled in the study (availability of MMP-9 reagents). The group was divided into two groups: patients with or without reduction of MMP-9 serum level. Of the 18 patients with baseline MMP-9 measured before CRT, a decrease of MMP-9 level was observed in 12 (67%) patients.

A comparison between the groups with and without the decrease of MMP-9 during CRT (significant differences) is presented in Table 5. Patients with normal, low CRP concentration at baseline were prone to respond to CRT by MMP-9 decrease.

A significant MMP-9 decrease was observed only in the group of patients with ischaemic aetiology of chronic HF (seven patients; 26,100 ± 7,624 pg/mL *vs* 23,360 ± 6,258 pg//mL

Table 3. Remodelling of cardiac chambers and valvular (mitral and tricuspid) function at baseline and during CRT

	Baseline	Six months of follow-up	P
LVEDD [mm]	71.2 ± 9.9	67.1 ± 10.4	< 0.05
LVESD [mm]	59.8 ± 11	54.8 ± 10.6	< 0.05
LVEDV biplane [mL]	273 ± 96	230 ± 84	< 0.05
LVESV biplane [mL]	205 ± 81	153 ± 68	< 0.05
RV FAC	0.32 ± 0.11	0.35 ± 0.12	NS
RVSP [mm Hg]	33 ± 21	30 ± 20	NS
TAPSE [cm]	1.45 ± 0.5	1.82 ± 0.6	< 0.05
LAA [cm^2]	27.1 ± 7	24.2 ± 8	0.06
MI jet area/LAA	0.33 ± 0.21	0.17 ± 0.4	< 0.05
MI EROA [cm^2]	0.3 ± 0.19	0.17 ± 0.14	< 0.05
RAA	19.7 ± 6.9	20 ± 5.9	NS
TI jet area/RAA	0.17 ± 0.18	0.07 ± 0.09	< 0.05
$E/E'_{(mean: septal and lateral)}$	24.4 ± 15	23 ± 16	NS

CRT — cardiac resynchronisation therapy; LVEDD, LVESD — left ventricular end-diastolic and end-systolic diameter; LVEDV, LVESV — left ventricular end-diastolic and end-systolic volumes; RV FAC — right ventricular fractional area change; RVSP — right ventricular systolic pressure; TAPSE — tricuspid annular peak systolic excursion; LAA, RAA — left/right atrial area; MI — mitral insufficiency; TI — tricuspid insufficiency; E — left ventricular early filling wave; E' — early diastolic maximum velocity of mitral annulus (mean value of lateral and septal)

after six months of CRT; p = 0.03). In the non-ischaemic group of chronic HF (11 patients), no change of MMP-9 was detected (27,931 ± 8,476 pg/mL *vs* 27,008 ± 7,361 pg/mL after six months of CRT; NS).

In patients with non-ischaemic aetiology of chronic HF, a longer LV pre-ejection period was observed in patients who would experience MMP-9 decrease at six months of follow-up (210 ± 40 *vs* 153 ± 45 ms; p < 0.05). Analysis of the whole MMP-9 subgroup revealed that the reduction in LV end-diastolic diameter (LVEDD) correlated well with the changes of MMP-9 level (r = 51; p = 0.03) and predicted the parallel MMP-9 decrease with sensitivity of 73% and a specificity of 83% (AUC 0.80; 95% CI 0.54–0.95; Fig. 2A). The baseline LA end-diastolic diameter measured in parasternal long-axis view ≤ 46 mm had a sensitivity of 83% and specificity of 67% in predicting MMP-9 decrease during CRT (AUC 0.83; 95% CI: 0.59–0.96; Fig. 2B). A significant correlation between baseline LA end-diastolic diameter and MMP-9 decrease was observed (r = 0.54; p = 0.02).

There was no significant correlation between the change of MMP-9 during CRT and dyssynchrony changes (for LV pre-ejection period, r = 0.36; for atrioventricular dyssynchrony, r = 0.11, for any intraventricular dyssynchrony parameter measured by velocity and strain, r ranged from 0.09 to 0.73; all NS).

The responder group was similar to the non-responders regarding both baseline MMP-9 level and MMP-9 change during CRT (26,266 ± 9,845 *vs* 25,862 ± 7,696 pg/mL; NS and –3,700 ± 4,986 *vs* –664 ± 4,814 pg/mL; NS).

Factors determining response rate

Greater baseline (atrio-, inter-ventricular) dyssynchrony was observed in the responders group (39 ± 9 *vs* 45 ± 9%; 152 ± ± 35 *vs* 187 ± 50 ms; both p < 0.05). Intra-LV baseline dyssynchrony differed significantly between the responders and the non-responders, especially in delay of time to peak myocardial systolic velocity of inferior and anterior wall (47 ± 37 *vs* 82 ± 52 ms; p < 0.05) (Table 6).

DISCUSSION

Our study showed that CRT causes favourable changes in haemodynamical parameters which correlate with some biochemical parameters including MMP. Also physical capacity improved in the majority of patients. The value of maximum ventilatory oxygen uptake is a well-known prognostic factor [9]. A similar group of patients was included in the PATH CHF II study. After six months of CRT, increases in maximum ventilatory oxygen uptake by 1.37 mL/kg/min and in six-minute walk test of 26 m were confirmed [10]. We achieved comparable functional improvement (i.e. increase by 3.7 mL/kg/min and 66 m, respectively).

Biochemical analysis

Similarly to other studies, the NT-proBNP level decreased significantly during follow-up [11]. The MMPs are key enzymes for the metabolism of extracellular matrix proteins. Under physiological conditions, MMPs are involved in extracellular degradation and breakdown of matrix proteins during normal tissue remodelling. Elevated MMP levels are associated with increased LV dimensions, and more advanced HF, of both ischaemic (post-myocardial infarction) and non-ischaemic origin [12–15]. A decrease of MMP level is perceived to be a favourable symptom of cellular remodelling [16]. Moreover, MMP-9 decrease has been documented in patients undergoing CRT, in whom ≥ 10% LVESV reduction was observed [17]. In our total population, no change of MMP-9 level was confirmed, although a significant decrease of MMP-9

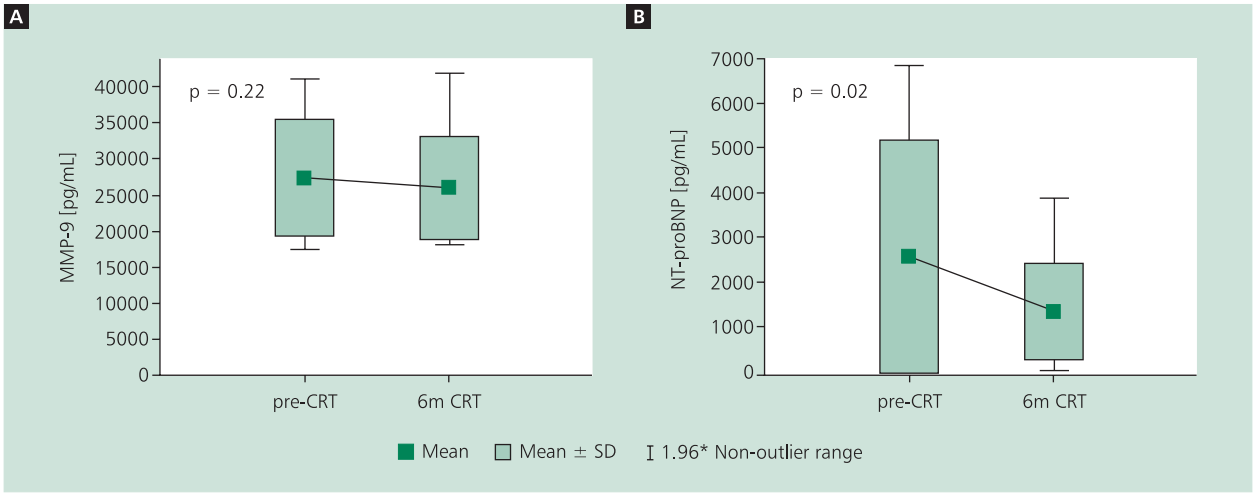

Figure 1. Changes of selected biochemical parameters following cardiac resynchronisation therapy (CRT); **A.** Change of matrix metalloproteinase-9 (MMP-9) serum level (before and after six months of CRT); **B.** Change of N-terminal pro-brain natriuretic peptide (NT-proBNP) serum level (before and after six months of CRT); 6m — six months of CRT

Table 4. Left ventricular mechanical dyssynchrony at baseline and during cardiac resynchronisation therapy

	Baseline	Six months of follow-up	P
Interventricular dyssynchrony [ms]	48 ± 45	15 ± 28	< 0.05
Atrio-ventricular dyssynchrony (left ventricle)	0.41 ± 0.09	0.48 ± 0.11	< 0.05
Apical four-chamber view:			
Time delay between the onsets of MSV of septal and lateral wall (dyssynchrony in basal segments) [ms]	50 ± 39	25 ± 29	< 0.05
Time delay between the onsets of MSV of septal and lateral wall (dyssynchrony in mid-segments) [ms]	61 ± 46	36 ± 34	< 0.05
Time delay between the peaks of MSV of septal and lateral wall (dyssynchrony in basal segments) [ms]	56 ± 39	45 ± 35	NS
Time delay between the peaks of MSV of septal and lateral wall (dyssynchrony in mid-segments) [ms]	68 ± 44	59 ± 35	NS
Apical two-chamber view:			
Time delay between the onsets of MSV of inferior and anterior wall (dyssynchrony in basal segments) [ms]	55 ± 36	27 ± 33	< 0.05
Time delay between the onsets of MSV of inferior and anterior wall (dyssynchrony in mid-segments) [ms]	55 ± 40	35 ± 31	< 0.05
Time delay between the peaks of MSV of inferior and anterior wall (dyssynchrony in basal segments) [ms]	67 ± 38	45 ± 34	< 0.05
Time delay between the peaks of MSV of inferior and anterior wall (dyssynchrony in mid-segments) [ms]	73 ± 50	50 ± 40	< 0.05
Apical three-chamber view:			
Time delay between the onsets of MSV of inferolateral and anteroseptal wall (dyssynchrony in basal segments) [ms]	44 ± 35	32 ± 41	NS
Time delay between the onsets of MSV of inferolateral and anteroseptal wall (dyssynchrony in mid-segments) [ms]	61 ± 42	38 ± 43	< 0.05
Time delay between the peaks of MSV of inferolateral and anteroseptal wall (dyssynchrony in basal segments) [ms]	59 ± 42	39 ± 45	< 0.05
Time delay between the peaks of MSV of inferolateral and anteroseptal wall (dyssynchrony in mid-segments) [ms]	67 ± 46	61 ± 49	NS

MSV — systolic myocardial velocity

Table 5. Comparison between subgroups with and without MMP-9 serum level reduction after six months of CRT (n = 18)

	Group with MMP-9 reduction	Group without MMP-9 reduction	P
Δ of LV lateral wall strain [%]	↑ 4.5 ± 5.5	↑ 2.2 ± 10.7	< 0.05
Intra-LV dyssynchrony: Δ time delay between the peaks of systolic strain of septum and LV lateral wall [ms]	↓ 67.9 ± 87	↓ 17 ± 36	< 0.05
Interventricular dyssynchrony: Δ delay of LV pre-ejection time [ms]	↓ 39 ± 44	↑ 35 ± 49	< 0.05
Δ LVEDD [mm]	↓ 6.7 ± 5.6	↓ 1 ± 4	< 0.05
LAEDD baseline [mm]	43.2 ± 6.6	51.2 ± 6.7	< 0.05
hs-CRP baseline [mg/L]	2.12 ± 1.6	4.7 ± 4.1	< 0.05
Haemoglobin baseline [mmol/L]	8.6 ± 0.6	9.2 ± 0.6	< 0.05

Δ — change during six months of cardiac resynchronisation therapy (CRT); LV — left ventricular; LVEDD — LV end-diastolic diameter; LAEDD — left atrial end-diastolic diameter; hs-CRP — high sensitive C-reactive protein; ↑ increase during six months of CRT; ↓ decrease during six months of CRT

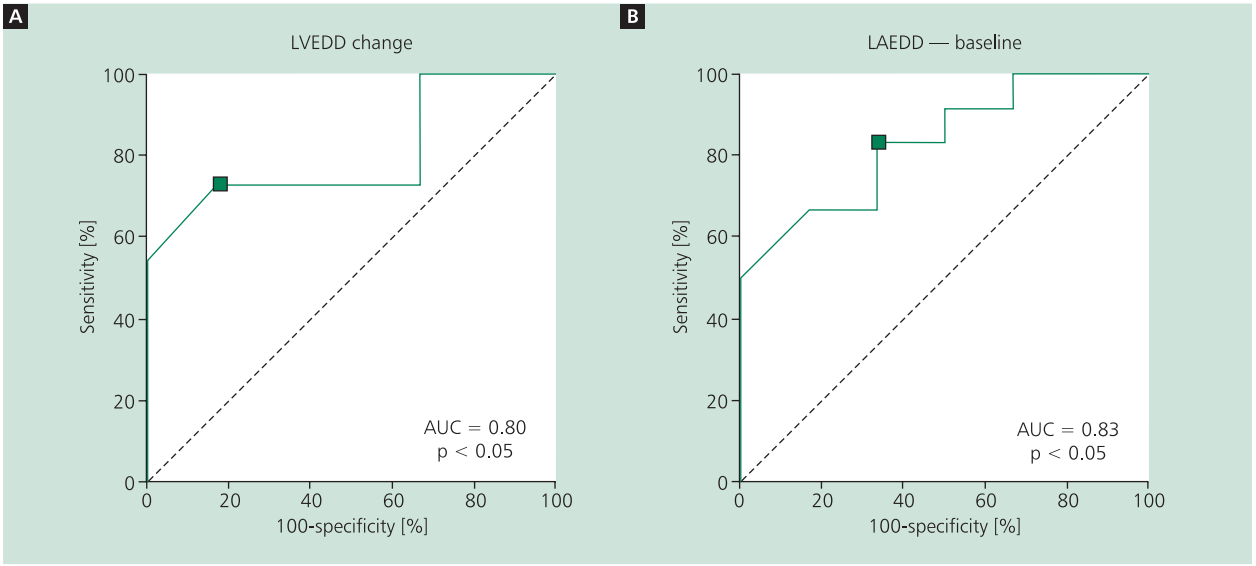

Figure 2. Receiver operating characteristics analysis of echocardiographic parameters in prediction of matrix metalloproteinase-9 (MMP-9) serum level decrease after cardiac resynchronisation therapy (CRT); **A.** Left ventricular end-diastolic diameter (LVEDD) change in prediction of MMP-9 serum level decrease during CRT; **B.** Left atrial end-diastolic diameter (LAEDD) at baseline in prediction of MMP-9 serum level decrease during CRT; AUC — area under curve

Table 6. Statistically significant differences in baseline dyssynchrony parameters between non-responders and responders to cardiac resynchronisation therapy

	Non-responders	Responders	P
LV pre-ejection period [ms]	152 ± 35	187 ± 50	< 0.05
Atrio-ventricular dyssynchrony [ms]	0.45 ± 0.09	0.39 ± 0.09	< 0.05
Intra-LV dyssynchrony between anterior and interior wall [ms]:			
In time to peak of MSV (in basal segments)	50 ± 35	75 ± 37	< 0.05
In time to onset of MSV (in mid-segments)	31 ± 25	65 ± 41	< 0.05
In time to peak of MSV (in mid-segments)	47 ± 37	82 ± 52	< 0.05

LV — left ventricular; MSV — myocardial systolic velocity

was noted in patients with ischaemic chronic HF treated with CRT.

The MMP-9 is an exceptional metalloproteinase (gelatinase) that is tightly linked to ischaemic processes in LV. It is released soon after myocardial infarction [14], persists and predicts late onset of chronic HF [13]. The MMP-9 activity is positively correlated with changes in LV volumes [18] and with wall motion index after infarction [19]. Sensitivity of MMP-9 to ischaemia is probably also responsible for its level changes under treatment (CRT).

Mechanical dyssynchrony analysis

In physiological conditions, ventricular activation lasts 80 ms (the duration of QRS complex) and finishes at anterior part of interventricular septum [20]. The ejection of LV and RV occurs almost simultaneously. Left bundle branch block (LBBB) induces the prolongation of LV and RV pre-ejection periods to 150 ms and 100 ms, respectively. In the studied group (the majority of patients with LBBB) these periods were longer, but interventricular delay was comparable to the one reported in the multicentre trial CARE-HF [21]. The median of interventricular dyssynchrony was 49.2 ms, while in our group it was 60 ms. Based on the CARE-HF results, it was concluded that patients with interventricular delay exceeding the given cut-off value (49.2 ms) undergoing CRT rarely reach the primary end-point (death, hospitalisation due to chronic HF decompensation, serious cardiovascular adverse event). In our population, it was not interventricular delay, but its component, the LV pre-ejection period, which was crucial in the prognosis of MMP-9 decrease. The LV pre-ejection period was one of the inclusion criteria in the CARE-HF study [21].

An intra-LV-dyssynchrony has been claimed to be the most important factor in patient selection to CRT [22]. Although echocardiographic dyssynchrony parameters are not CRT inclusion criteria as recommended by international cardiology associations, most studies evaluating favourable response to CRT have used echocardiographic dyssynchrony parameters rather than QRS complex duration [23]. In our study, two tissue Doppler applications were used: velocity and strain assessment.

In the early studies, based on the assumption that the lateral wall is the most delayed in LV systole, dyssynchrony between septum and LV lateral wall was measured [24]. Later publications engaged further walls in the dyssynchrony measurements, and additionally medial segments were assessed. In seeking a unified parameter, Yu et al. [25] introduced the tissue Doppler-derived dyssynchrony index: standard deviation of 'time to peak of myocardial systolic velocity' in 12 LV segments. The inferiority of strain analysis was evidenced by the same author [26]. In our population, we were not able to show any prognostic value of strain temporal parameters either. Nevertheless, the use of any measurement describing the regional function of LV before CRT was seriously questioned after the release of the PROSPECT study results, which revealed poor reproducibility and high variability among centres [27]. Nonetheless, easily-acquired parameters, such as LV pre-ejection period or atrio-ventricular dyssynchrony, may still be used.

Limitations of the study

These results definitely need further studies. In the MMP-9 analysis, we have evaluated a small number of patients, that might influence the results. Therefore it is difficult to exclude the possibility that some statistically significant or non-significant relations might have occurred by chance (e.g. no difference in MMP-9 levels between responders and non-responders).

To make the response definition more objective, and to avoid the complexity of the data presentation in our moderately small group, we decided not to include any clinical criteria and to consider only LVESV reduction of $\geq$ 10% (not 15% due to relatively short-term six-month follow-up) as a response definition.

CONCLUSIONS

Cardiac resynchronisation therapy results in the MMP-9 level reduction in ischaemic chronic HF patients. Among patients who responded to CRT by MMP-9 decrease, lower CRP concentration at baseline was observed. The reduction of MMP-9 level may be predicted by baseline left atrial end-diastolic diameter, and correlates well with LVEDD change during CRT.

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Conflict of interest: *Dr Radosław Lenarczyk has received consulting fees from Biotronic and Medtronic; the remaining authors have no conflicts of interest to disclose.*

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Echokardiograficzna kwalifikacja i ocena odpowiedzi na terapię resynchronizującą wśród pacjentów z przewlekłą niewydolnością serca. Metaloproteinaza macierzy zewnątrzkomórkowej-9 — subanaliza

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Streszczenie

Wstęp: Terapia resynchronizująca (CRT) jest oparta na koncepcji synchronicznej stymulacji prawej i lewej komory (LV) u pacjentów z zaawansowaną przewlekłą niewydolnością w przebiegu dysfunkcji skurczowej LV i poszerzonym zespołem QRS ≥ 120 ms. Korzystna odpowiedź na CRT jest definiowana za pomocą klinicznych i echokardiograficznych kryteriów. Zmiany stanu pacjenta na poziomie biochemicznym (peptydy natriuretyczne, metaloproteinazy macierzy zewnątrzkomórkowej) wymagają przeprowadzenia dalszych badań.

Cel: Celem pracy była analiza klinicznych, hemodynamicznych i biochemicznych zmian pod wpływem CRT oraz znalezienie czynników determinujących korzystną odpowiedź na CRT.

Metody: Do badania włączono 50 pacjentów ze skurczową niewydolnością serca (NYHA IV — 2 pacjentów), poszerzonym zespołem QRS (160 ± 31 ms) i obniżoną frakcją wyrzutową LV (26 ± 5,8%), optymalnie leczonych farmakologicznie, u których zastosowano CRT. Analizie poddano dane echokardiograficzne (z włączeniem doplera tkankowego) i biochemiczne (NT-proBNP i CRP) zebrane przed terapią i po 6 miesiącach CRT. Stężenie metaloproteinazy macierzy zewnątrzkomórkowej-9 (MMP-9) oceniono w podgrupie 18 pacjentów. Korzystną odpowiedź na CRT definiowano jako spadek objętości końcowoskurczowej LV o 10% w porównaniu z wartością wyjściową.

Wyniki: Na CRT korzystnie odpowiedziało 35 (70%) pacjentów. Pod koniec obserwacji zarejestrowano poprawę maksymalnego zużycia tlenu w teście spiroergometrycznym (VO_2, z 12,9 ± 3,8 do 16,6 ± 4,7 ml/kg/min; $p < 0,05$), zmniejszenie stężenia NT-proBNP (z 2579 ± 2598 do 1339 ± 1088 pg/ml; $p < 0.05$) oraz redukcję dyssynchronii między-, przedsionkowo- i śródkomorowej. Przed CRT większą dyssynchronię zaobserwowano w grupie korzystnej odpowiedzi na CRT. Obniżenie stężenia MMP-9 zanotowano u 12 (67%) pacjentów, w tym istotne statystycznie wśród osób z niedokrwienną etiologią niewydolności serca (26 100 ± 7624 pg/ml *v.* 23 360 ± 6258 pg/ml; $p = 0,03$). W grupie pacjentów z redukcją MMP-9 stwierdzono niższe wyjściowe stężenie CRP (2,12 ± 1,6 *v.* 4,7 ± 4,1 mg/l). Zmniejszenie wymiaru końcoworozkurczowego LV korelowało ze zmianami MMP-9 ($r = 51$; $p = 0,03$). Wymiar lewego przedsionka przed CRT mierzony w przymostkowej osi długiej ≤ 46 mm z 83-procentową czułością i 67-procentową swoistością przewidywał spadek stężenia MMP-9 (AUC 0,83; 95% CI 0,59–0,96).

Wnioski: Terapia resynchronizująca powoduje korzystną przebudowę mięśnia sercowego ze zmniejszeniem stężenia NT-proBNP, poprawę funkcji globalnej i regionalnej komór serca i redukcję stężenia MMP-9 wśród pacjentów z niedokrwienną niewydolnością serca. Zmiany stężenia MMP-9 podczas CRT dobrze korelują ze zmianami wymiaru końcoworozkurczowego LV i można je przewidywać, oceniając wyjściowy wymiar lewego przedsionka.

Słowa kluczowe: terapia resynchronizująca, metaloproteinazy, niewydolność serca, echokardiografia

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