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THE RELATIONSHIP OF MYOCARDIAL COLLAGEN METABOLISM AND REVERSE REMODELING AFTER CARDIAC RESYNCHRONIZATION THERAPY

ODNOS IZMEĐU METABOLIZMA MIOKARDIJALNOG KOLAGENA I REVERZNOG REMODELOVANJA POSLE SRČANE RESINHRONIZACIONE TERAPIJE

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Summary

Background: In the majority of patients with a wide QRS complex and heart failure resistant to optimal medical therapy, cardiac resynchronization therapy (CRT) leads to reverse ventricular remodeling and possibly to changes in cardiac collagen synthesis and degradation. We investigated the relationship of biomarkers of myocardial collagen metabolism and volumetric response to CRT.

Methods: We prospectively studied 46 heart failure patients (mean age 61±9 years, 87% male) who underwent CRT implantation. Plasma concentrations of amino-terminal propeptide type I (PINP), a marker of collagen synthesis, and carboxy-terminal collagen telopeptide (CITP), a marker of collagen degradation, were measured before and 6 months after CRT. Response to CRT was defined as 15% or greater reduction in left ventricular end-systolic volume at 6-month follow-up.

Results: Baseline PINP levels showed a negative correlation with both left ventricular end-diastolic volume (r=-0.51; p=0.032), and end-systolic diameter (r=-0.47; p=0.049). After 6 months of device implantation, 28 patients (61%) responded to CRT. No significant differences in the baseline levels of PINP and CITP between responders and non-responders were observed (p>0.05 for both). During follow-up, responders demonstrated a significant increase in serum PINP level from 31.37±18.40 to 39.2±19.19 μg/L (p=0.049), whereas in non-responders serum PINP levels

Kratak sadržaj

Uvod: Kod većine pacijenata sa širokim QRS kompleksom i srčanim oboljenjima rezistentnim na optimalnu medicinsku terapiju, srčana resinhronizaciona terapija (CRT) dovodi do reverznog remodelovanja leve komore i potencijalno do promena u sintezi i degradaciji srčanog kolagena. Istraživali smo odnos između biomarkera metabolizma miokardijalnog kolagena i volumetrijskog odgovora na SRT.

Metode: Prospektivno smo proučavali 46 pacijenata sa srčanim oboljenjima (prosečne starosti 61±9 godina, 87% muškog pola) koji su podvrgnuti implantaciji SRT. Koncentracije amino-terminalnog propeptida tipa I (PINP) u plazmi, markera sinteze kolagena, kao i karboksi-terminalnog telopeptida kolagena (CIPT), markera degradacije kolagena, izmereni su pre i 6 meseci posle početka SRT. Odgovor na SRT definisan je kao smanjenje od 15% ili više end-sistolnog volumena leve komore prilikom pregleda posle 6 meseci.

Rezultati: Početni nivoi PINP pokazali su negativnu korelaciju sa end-diastolnim volumenom leve komore (r=-0,51; p=0,032) kao i end-sistolnim prečnikom (r=-0,47; p=0,049). Šest meseci nakon ugradnje uređaja, 28 pacijenata (61%) dalo je odgovor na SRT. Između početnih nivoa PINP i CITP kod pacijenata koji su odgovorili i onih koji nisu odgovorili na terapiju nisu uočene značajne razlike (p>0,05 za oba). Tokom praćenja pacijenata, oni koji su pokazali odgovor na terapiju imali su i značajan porast nivoa PINP u serumu sa

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List of abbreviations: CRT, cardiac resynchronization therapy; PINP, amino-terminal propeptide type I; CITP, carboxy-terminal collagen telopeptide; ECM, extracellular matrix; NYHA, New York Heart Association; 6MWT, six minute walk test; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; NT-proBNP, amino-terminal pro-brain natriuretic peptide; DCM, dilated cardiomyopathy; LVAD, left ventricular assist device; MMPs, matrix metalloproteinases.

did not significantly change (from 28.12±21.55 to 34.47± 18.64 μg/L; p=0.125). There were no significant changes in CITP levels in both responders and non-responders (p>0.05).
Conclusions: Left ventricular reverse remodeling induced by CRT is associated with an increased collagen synthesis in the first 6 months of CRT implantation.

Keywords: collagen metabolism, cardiac resynchronization therapy, reverse remodeling

31,37±18,40 na 39,2±19,19 μg/L (p=0,049), dok se kod pacijenata kod kojih nije bilo odgovora nivoi PINP u serumu nisu značajno promenili (sa 28,12±21,55 na 34,47±18,64 μg/L; p=0,125). Nije bilo značajnih promena u nivoima CITP ni u jednoj grupi pacijenata (p>0,05).
Zaključak: Reverzno remodelovanje leve komore izazvano srčanom resinhronizacionom terapijom povezano je s povećanom sintezom kolagena u prvih šest meseci posle implantacije SRT.

Ključne reči: metabolizam kolagena, srčana resinhronizaciona terapija, reverzno remodelovanje

Introduction

The cardiac extracellular matrix (ECM) is a dynamic system able to adapt to the conditions of increased pressure and volume, myocardial infarction and cardiomyopathy. The main structural protein of the ECM is collagen constituting approximately 2–4% of a healthy adult human heart (1). Abundant collagen synthesis leads to myocardial hypertrophy and fibrosis (2, 3), while excessive degradation and loss of collagen support leads to chamber dilatation, probably due to inadequate support of the myocytes (4–8). The process of collagen synthesis begins in fibroblasts, which produce procollagen and release it in the extracellular space. In the ECM, amino-terminal propeptides (PINP and PIIINP) and carboxy-terminal propeptides (PICP and PIIICP) are separated by endopeptidases, released into the circulation and can be used as serum markers of collagen synthesis (9). Degradation of type I collagen is influenced by proteolytic enzymes, mainly matrix metalloproteinases and catepsins. During that process carboxy-terminal telopeptide of type I collagen (CITP) is released, and can be used as a marker of collagen degradation (2, 10–13).

Cardiac resynchronization therapy (CRT) is an established treatment option for heart failure patients with a widened QRS complex who are resistant to optimal medical therapy (14–16). CRT device implantation may lead to left ventricular (LV) reverse remodeling, systolic and diastolic function improvement and reduction of mitral regurgitation (17–18). Left ventricular remodeling contributes to reduction of symptoms and improvement of exercise tolerance, quality of life and overall survival (19–21).

As the process of remodeling in heart failure is primarily related to changes in cardiomyocytes and extracellular matrix (ECM), LV volume reduction after CRT implantation may be associated with cellular changes (22, 23). It is assumed that cellular reverse remodeling represents a gradual process that begins by reducing inflammation and it takes about 6 months to become evident (22). However, previous studies investigating CRT-induced changes in collagen metabolism are not consistent, as CRT implantation has been reported to increase, decrease or have no effect on collagen synthesis (24–26).

The aim of this study was to investigate the relationship of the biomarkers of collagen metabolism and volumetric response to CRT.

Materials and Methods

We recruited 46 consecutive patients with chronic heart failure undergoing CRT implantation according to guideline-proposed criteria (27). The group consisted of 40 men (87%) and 6 women (13%). Selection criteria for CRT implantation included New York Heart Association (NYHA) functional class III or IV, left ventricular ejection fraction (LVEF) ≤35% and complete left bundle branch block with QRS duration >120 ms. All patients were on optimal medical therapy for at least 3 months before CRT implantation. Exclusion criteria were decompensated heart failure, myocardial infarction within 3 months prior to CRT implantation, prior pacemaker implantation, acute myocarditis, end stage renal disease and severe chronic obstructive pulmonary disease. All patients underwent transthoracic echocardiography, clinical evaluation and biomarkers measurement before CRT implantation and 6 months thereafter. Clinical characteristics included assessment of the New York Heart Association (NYHA) class (28), quality of life using »Minnesota Living with Heart Failure« questionnaires (29), and functional capacity according to the six minute walk test (6MWT) (30).

The study was approved by the local Research Ethics Committee and all subjects gave their written informed consent.

Echocardiographic examination

Standard two-dimensional (2D) and color Doppler transthoracic echocardiography was performed to estimate LV volumes and LVEF prior to CRT implantation and 6 months thereafter. Examinations were done using a commercially available system (Mylab 60, Esaote, Italy). Patients were imaged in the left lateral decubitus position, using a 3.5 MHz transducer, from standard parasternal and apical views. Left ventricular volumes and LVEF were estimated using the biplane Simpson's technique. Response to CRT was

defined as 15% or greater reduction in LV end-systolic volume from baseline to 6-month follow-up.

Pacemaker implantation

All patients received a biventricular pacemaker by transvenous LV lead placement. Retrograde coronary sinus cannulation with selective venography was obtained in order to visualize main venous branches and to position LV epicardial lead appropriately (preferably in a postero-lateral vein). The right atrial and ventricular leads were positioned conventionally. Atrioventricular delay optimization was performed by echocardiography in order to provide the longest filling time for completion of the end-diastolic filling flow before LV contraction.

Biochemical analysis

Fasting blood samples were obtained from every patient just before CRT implantation and after six months of follow-up. Procollagen type I amino-terminal propeptide (PINP) was measured using electrochemiluminescence (Elecsys, Roche, Mannheim, Germany). Assay sensitivity was 5 μg/L, with intra-assay and inter-assay coefficients of variation (CV) of 3.1% and 3.5%, respectively. Carboxy-terminal telopeptide of type I collagen (CITP) was determined by electrochemiluminescence (Elecsys, Roche). Assay sensitivity was 0.01μg/L, with intra-assay and inter-assay CV of 4.2% and 4.7%, respectively. Amino-terminal pro-brain natriuretic peptide (NT-proBNP) was measured in serum samples by the enzyme-linked immunosorbent assay (ELISA) method.

Statistical analysis

Continuous variables are expressed as mean± standard deviation (SD) and compared using Student t-test or Mann-Whitney test. Proportions were compared using chi-square test and Fisher's exact test. The Spearman two-way test was used to assess the correlation between two quantitative variables and non-normal distribution. The Pearson two-way test was used to assess the correlation between two normally distributed quantitative variables. For all tests, a P value <0.05 was considered significant.

Statistical analysis was performed using commercially available software (SPSS version 17.0, SPSS Inc. Chicago, Illinois).

Results

Baseline patient clinical characteristics are presented in *Table I*. A total of 46 patients (mean age 61±9 years, 87% men) were included. Twenty-eight patients (61%) showed significant reverse remodeling and were regarded as responders. Patients who did not respond to CRT more frequently had ischemic cardiomyopathy (100 vs. 36%, p=0.033) and had a significantly higher baseline LVEF (31±4) than those who responded to CRT (24±6; p=0.008). In addition, non-responders tended to more frequently have diabetes mellitus and a higher body mass index, but those differences did not reach statistical significance (*Table I*).

Patients who responded to CRT showed a significant improvement in NYHA class (p=0.003), 6-minute walking distance (292±55 to 365±107 m, p=0.012), and quality of life (41.3±19.2 to 20.6±22.8, p=0.026). Responders also showed a significant increase of LVEF (from 24±6 to 41±11%, p<0.001), and significant decrease in LV dimensions (*Table II*). There were no significant changes in echocardiographic parameters in patients who did not respond to CRT.

However, non-responders also showed a significant improvement in quality of life (from 53.2±18.4

Table I Baseline characteristics of the study population.

	All patients (n=46)	Responders (n=28)	Non-responders (n=18)	P-value
Age, years	61±9	60±11	64±7	0.315
Male sex, n (%)	40 (87)	26 (93)	14 (78)	0.823
BMI (kg/m^2)	27.1±3.8	25.8±4.0	28.7±3.2	0.096
Ischemic etiology, n (%)	28 (61)	10 (36)	18 (100)	0.033
QRS width, ms	161±23	165±23	157±24	0.411
Hypertension, n (%)	34 (78)	20 (77)	14 (78)	0.884
Dyslipidemia, n (%)	14 (30)	6 (23)	8 (44)	0.376
Diabetes mellitus, n (%)	14 (30)	4 (15)	10 (56)	0.074
Smoking, n (%)	20 (44)	8 (31)	12 (67)	0.192

BMI – Body mass index

Table II Echocardiographic parameters and cardiac biomarkers at baseline and after 6 months of CRT implantation.

	Responders (n=28)		Non-responders (n=18)	
	Baseline	Follow-up	Baseline	Follow-up
LVEF, %	24±6	41±11*	30.7±4	37±8
LV EDD, mm	74±8	64±8*	70.4±8.4	69±8
LV ESD, mm	62±10	49±11*	60±9	57±9
LV EDV, mL	253±91	193±70*	204±65	228±80
LV ESV, mL	192±77	117±70*	141±52	149±61
PINP, μg/L	31.37±18.4	39.2±19.19*	28.12±21.55	34.47±18.64
CITP, μg/L	0.53±0.40	0.450±0.33	0.396±0.23	0.447±0.33
NTproBNP, pg/mL	3267±2932	3553±4971	2222±1025	7585±2656*

* denotes $p<0.05$ from baseline; LVEF – left ventricular ejection fraction; LVEDD – left ventricular end-diastolic diameter; LVESD – left ventricular end-systolic diameter; LVEDV – left ventricular end-diastolic volume; LVESV – left ventricular end-systolic volume; PINP – amino-terminal propeptide of type I collagen; CITP – carboxy-terminal telopeptide of type I collagen; NTproBNP – N-terminal pro-brain natriuretic peptide.

to 29.4±18.6, p=0.005). Nonetheless, serum levels of NT-proBNP did not significantly change in the responders (from 3267±2932 to 3553±4971 pg/ml, p=0.808), in contrast to the non-responders in whom NT-proBNP significantly increased during the follow-up (2222±1025 to 7586±2656 pg/mL, $p<0.001$) (*Table II*).

Markers of collagen metabolism and response to CRT

No significant differences in the baseline levels of PINP, CITP or NT-proBNP between responders and non-responders were observed (*Table II*). Men had a lower serum PINP level at baseline compared to women, but the difference was not significant (28.13± 17.1 to 34.6±19.3 μg/L, p=0.107). Baseline PINP levels showed a negative correlation with both LV end-diastolic volume (r=-0.51; p=0.032), and end-systolic diameter (r=-0.470; p=0.049).

After 6 months of follow-up, serum PINP levels increased from 31.37±18.40 to 39.2±19.19 μg/L, p=0.049), while no significant changes were observed in non-responders (from 28.12±21.55 to 34.47±18.64 μg/L, p=0.125). There were no significant changes in serum CITP levels in both responders (from 0.53±0.40 to 0.450±0.33 μg/L, p=0.753) and non-responders (from 0.396±0.23 to 0.447±0.33 μg/L, p=0.504) (*Table II*).

Discussion

Our study demonstrated that volumetric response to CRT, defined as LV reverse remodeling, was associated with a significant increase of PINP levels during the first 6 months of device implantation. Baseline PINP levels were similar in responders and non-responders and showed negative correlation with end-diastolic LV volume and end-systolic diameter.

Cardiac resynchronization therapy reduces mechanical interventricular dyssynchrony between the right and left ventricles and intraventricular dyssynchrony within the left ventricle (31). Reduced intraventricular dyssynchrony improves LV global function, by increasing the LV filling time, decreasing septal dyskinesis, and reducing mitral regurgitation (31). These immediate mechanical changes are accompanied by long-term changes in myocardial structure, particularly ECM (22, 23). Previous reports on CRT-induced changes in myocardial collagen synthesis are conflicting (24–26). Our data support prior reports suggesting that reverse remodeling after CRT implantation is accompanied by significant changes in myocardial ECM structure. Collagen type I is the major protein in the ECM ensuring structural integrity, while its insufficiency leads to impaired contractility, wall thinning, and the LV dilatation (1, 4–6). The regulation of ECM remodeling, i.e., the balance between collagen synthesis and degradation, is essential for normal cardiac structure and function (4–6). The increase in collagen synthesis rate in our study was accompanied by a reduction of LV volumes and contractile function improvement after 6 months of CRT therapy and could be, therefore, interpreted as a surrogate marker of reverse remodeling.

Our data are in line with a study by Umar et al. who reported a significant increase of PINP and PIINP levels 6 months after CRT implantation (24). By contrast, another study measuring carboxyterminal

propeptide (PICP) before and one year after CRT implantation reported a statistically significant decrease in the markers of collagen synthesis (25). Finally, in a study published by Lopez-Andres et al, no significant changes in PINP, PIIINP or ICTP levels were observed either 3 or 18 months after CRT implantation (26).

In similarity to the CRT patient population, a significant increase in the PINP and PICP concentrations was also observed in patients with dilated cardiomyopathy (DCM) who underwent left ventricular assist device (LVAD) implantation, one month after device implantation (32). In a study by Bruggink et al. (33) the authors monitored levels of PINP, PIIINP and CITP in 26 patients before LVAD implantation, after one, three and six months following device implantation, and just before heart transplantation. A significant increase of PINP and PIIINP levels was observed over the first 200 days after implantation of LVAD, with a gradual decrease at farther time points. Importantly, these changes were followed by initial increase and subsequent decrease of the extracellular matrix volume estimated from myocardial biopsy samples. Thus, reverse remodeling induced by improvement of LV loading condition after LVAD implantation was accompanied by an increase in collagen synthesis over the first 6 months (33).

The CITP levels, a marker of collagen degradation, were higher in patients with DCM before LVAD implantation compared to healthy subjects (33). After device implantation, these levels tended to decrease. However, in our study group no significant changes of CITP levels were observed. The degradation of collagen is regulated by the group of matrix metalloproteinases (MMPs), particularly collagenase, MMP-1 and gelatinases MMP-2 and MMP-9 (34–35). Carboxyterminal telopeptide-CITP is released during the hydrolysis of the collagen type I by MMP-1 (6).

Results of previous studies have shown that patients with dilated cardiomyopathy (CMP) have increased concentrations of MMP-1 and MMP-1/TIMP1 ratio compared to the control group. MMP-1 and MMP- /TIMP1 were positively correlated with LVEDV, and negatively with cardiac index (35). Li et al. reported that after LVAD implantation MMP1 levels decreased (34). As reported in previous studies, the levels of NTproBNP significantly increased in the non-responder group of patients (36). It therefore seems that structural myocardial changes influenced by CRT and LVAD implantation are very similar, but more intense with the LVAD. However, despite both being reserved for terminal heart failure patients, LVAD and CRT have distinctly different mechanisms of action and are not indicated for the same patient populations.

Our data indicate that LV reverse remodeling, i.e. LV end-systolic volume reduction, after CRT implantation is related to enhanced myocardial collagen synthesis; however, our inferences are limited by the small sample size and further studies with larger study populations seem warranted.

Conclusions

The marker of myocardial collagen synthesis amino-terminal propeptide type I (PINP) is inversely correlated to left ventricular volumes and dimensions in patients undergoing CRT. Left ventricular reverse remodeling induced by CRT is associated with both significant improvement in patients' functional status and an increase in markers of myocardial collagen synthesis in the first 6 months after CRT implantation.

The investigated biomarkers are only indirect measures of myocardial collagen metabolism and may be affected by metabolism in other organ systems and by other metabolic factors. Therefore, the relationship of myocardial collagen metabolism and reverse remodeling after CRT should ideally be investigated by invasive myocardial biopsy to assess CRT-related myocardial fibrosis and tissue repair.

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Conflict of interest statement

The authors stated that they have no conflicts of interest regarding the publication of this article.

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