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Original Article

Evaluation of the relationship between dyssynchrony and myocardial fibrosis markers in patients with cardiac resynchronization therapy

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Abstract

Aim: Dyssynchrony can be seen in some patients with heart failure. The goal of cardiac resynchronization therapy (CRT) is the correction of dyssynchrony. The correction of myocardial loading and remodel-ing prevents development of the myocardial fibrosis. The aim of this study is to evaluate myocardial fibrosis markers in patients with heart failure CRT applied and to assess the relationship between these markers and dyssynchrony.

Material and Methods: Fifty one patients (ejection fraction (EF) ≤ % 35, QRS duration ≥130 msec) were included into the study. Electrocardiography (ECG), 6 minute walking test, and echocardiography were applied before and 6 months after CRT to all patients. Furthermore, Type I Collagen C-Terminal Propeptide (PICP), Type I Collagen C-Terminal Telopeptide (ICTP) levels and PICP/ICTP ratio were studied as myocardi-al fibrosis markers in blood samples.

Results: It is observed that QRS was shortened after CRT (p=0.0001). Six minute walking distance was in-creased 6 months after CRT (p=0.0001). PICP level measured before CRT as 560.2 ± 300.4 µg/L while it is measured as 476,9±285,8 µg/L 6 months after CRT (p=0.004). PICP/ICTP ratio before and 6 months after CRT was 9.7 ± 10 and 37.1 ± 32.8 respectively (p=0.0001). It is determined a negative relationship between EF and PICP level and PICP / ICTP ratio (p=0.008, r = -0.37).

Conclusion: Our results show that CRT reduces the left ventricular dyssynchrony and consequently leads to favor-able changes in myocardial fibrosis markers. Reducing the mechanical stresses on left ventricle and returning of consequent remodeling may be one of the important mechanisms in the prevention of cardiac fibrosis.

Keywords: Cardiac resynchronization therapy; dyssynchrony; myocardial fibrosis

INTRODUCTION

Intraventricular conduction abnormalities associated with systolic dysfunction are often observed in patients with chronic heart failure. The frequency of QRS duration longer than 130 ms is 25-50 % and fre-quency of left bundle branch block (LBBB) is 15-27% in patients with heart failure (1). These findings cause ventricular dyssynchrony and this in turn causes a decrease in ventricular functions, remodeling of the left ventricle and progression of heart failure and eventually leads to a pathophysiologic process which in-creases morbidity and mortality. Cardiac resynchronization therapy (CRT) is one of the treatment options in these patients (2). CRT enables correction of disruption of left ventricular functions due to atrioventric-ular, interventricular and intraventricular conduction delay by means of cardiac stimulation method (3). The CRT may be able to reverse remodeling by amelioration of dyssynchrony. This effect of CRT starts after 3 to 9 months, and continues until the 18th month (4). CRT decreases myocardial fibrosis by its ef-fects on collagen synthesis (5).

Aim of this study is to determine dyssynchrony parameters before and 6 months after CRT in patients who are symptomatic despite optimal medical treatment and cardiac resynchronization therapy is planned according to guidelines and to determine Type I Collagen C- Terminal

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Propeptide (PICP) and Type I Collagen C-Terminal Telopeptide (ICTP) levels in serum samples and PICP/ICTP ratio, which are consid-ered to be markers of myocardial fibrosis, and to evaluate the effects of CRT on markers of myocardial fibrosis.

MATERIAL and METHODS

Study Population

51 patients who were admitted at the Cardiology Department of Cukurova University (between 2013 and 2015 years), who were eligible for CRT indications according to current guidelines (6), who had NYHA class II, III and ambulatory IV heart failure symptoms in spite of optimal medical treatment, Ejection fraction (EF) ≤ 35 % and QRS duration >130 ms in those with LBBB in the electrocardiogram (ECG) and >160 ms in those without LBBB in ECG were included into the study. Basal demographic characteristics of all patients were determined, along with medication use, functional capacity, age, gender, diabetes mellitus, hyper-lipidemia, hypertension, family history of coronary artery disease and other comorbidities. After a com-prehensive physical examination, 12 derivation ECGs were obtained, detailed echocardiographic exami-nation and 6 minute walking test was done to patients meeting appropriate criteria before CRT, and PICP, ICTP levels and PICP-ICTP ratios were determined as serum markers. These same investigations were done 6 months after CRT.

Exclusion Criteria

- Patients not having optimal medical treatment for heart failure (HF)
- Patients having NYHA class I functional capacity
- QRS < 130 ms
- Life expectation shorter than one year due to non-cardiac causes
- Patients with advanced chronic renal failure
- Patients with hepatic failure or hepatic fibrosis
- Patients with osteoporosis
- Patients with unsuccessful CRT implantation
- Patients refusing to give written informed consent were excluded.

Echocardiography

Detailed transthoracic echocardiographic examinations were done to the patients before and 6 months after CRT. This investigation was used parasternal long short axis and apical two and four chambers imag-es with 2.5-3.5 MHz transducer at the left lateral position with a General Electric VIVID S5 model (serial number 050569VS 5N) echocardiography device. M-mode, two-dimensional examination and Doppler (pulsed wave (PW), color Doppler and tissue Doppler) techniques were used in echocardiographic evalua-tion. Ejection fraction was calculated by Teicholz method with M-mode in parasternal long-axis. End dias-tolic and systolic volumes were calculated according to the modified Simpson method, from apical four chamber images (7). The time period between contractions of the septum and posterior wall at the papil-lary muscle level at parasternal short axis was calculated as septum posterior wall movement delay (SPWD) (8). Duration longer than 130 ms was considered as a marker of intraventricular dyssynchrony. The durations between initiation of QRS and initiation of ejection at aortic and pulmonary valve levels by PW Doppler were measured as aortic and pulmonary preejection times. The difference between aortic preejection and pulmonary preejection times was measured as interventricular mechanic delay (IVMD). This duration being 40 ms or longer or aortic preejection time being longer than 140 ms were considered as markers of interventricular dyssynchrony (9,10). Tissue Doppler measurements of the PW were done at basal septum and basal lateral segments just above the attachment of the septal leaflet of the mitral valve to the annulus. The duration of time between initiation of QRS and peak systolic velocity, by PW tissue Doppler at apical four chamber by sample volume on septal and lateral mitral annulus. A delay be-tween lateral wall and septum of 60 ms or more was considered as intraventricular dyssynchrony (11). The duration of time between peak velocities of the septum and lateral wall was calculated by placing the sample volume to basal segments of the septum and lateral walls. Duration of 65 ms or more was also considered as intraventricular dyssynchrony (12).

Blood Tests

Blood samples were obtained from antecubital veins of patients in sterile conditions at the supine posi-tion after a resting period of 30 minutes and blood tests (whole blood count, blood chemistry and thyroid function test) were done. Also, PICP (Algen, Sunredbio, CA, USA) and ICTP (Algen, Cusabio, China) levels of serum samples were measured with commercial kits by Enzyme Linked Immunosorbent Assay (ELISA) method.

Device Implantation

After appropriate local preparations, a pacemaker pocket was created via a left pectoral incision and left subclavian vein punction was done. Defibrillation electrode was placed at the apex of the right ventricle. The left ventricle electrode was placed on the posterolateral branch of the coronary sinus. Pacing and sensing functions of all electrodes were tested. Medtronic, St Jude and Biotronik brand devices and CRT-D compatible transvenous double strand defibrillation lead systems were used in this study.

Ethics committee approval

This study was approved by the Ethics Committee of Cukurova University with the protocol number of TTU-2015-4909.

Statistical analysis

The IBM SPSS Statistics Version 17.0 software package was used to statistically analyze the data. Categorical measurements were summarized as number and percentage, and continuous measurements were reported as mean and standard deviation (median and minimum-maximum when necessary). Distributions were controlled in the comparison of continuous measurements of groups, and Mann Whitney U test was used when parametric distribution precondition was not met. Wilcoxon test and Analysis of Vari-ance of Repeated Measurements were used in the comparison of time-dependent test results. A statisti-cal significance level of 0.05 was used for all tests.

RESULTS

Cardiologic findings before and 6 months after CRT of 51 patients were examined in this study. The base-line characteristics of the patients were given in Table 1. While the median 6 minute walking distance was 238 m (70-460) before CRT, it was found to be median 335 m (175 - 570) after CRT (p=0.0001). The mean QRS duration of patients before CRT was 165.7±29.5 ms; and 6 months after CRT the mean QRS duration was 133.5±26.4 ms (p=0.0001). The median PICP measurement value of patients before CRT was 475,9 µg/L (134.4-1200 µg/L) and median PICP measurement value 6 months after CRT was 425.3 µg/L (191.6-1200 µg/L) (p=0.004). The decrease in PICP measurement value after treatment was statistically signifi-cant. The median ICTP measurement value of patients before CRT was 12.2 µg/L (1-40 µg/L) and median ICTP measurement value 6 months after CRT was 15 µg/L (3.7-40 µg/L)(p=0,173). In the comparison of ICTP measurement values before and 6 months after CRT, no statistically significant differences were found. The median PICP/ICTP Ratio measurement value of patients before CRT was 46.8 (7.7-525.5) and the median ratio value 6 months after CRT was 28 (6.8-173.5) (p=0.0001). The mean EF value of patients was 28.9±4.2 before CRT, and the mean EF value 6 months after CRT was 34.8±7.3 (p=0.0001). The left ventricular end diastolic diameter (LVEDD), left ventricular end systolic diameter (LVESD) and septal pos-terior wall mechanical delay (SPWD) measurement were found to show a statistically significant decrease 6 months after CRT (p=0.0001). The median interventricular delay time value of patients before CRT was 43 ms (10-87 ms) and the median interventricular delay time value 6 months after CRT was 31 ms (5-68) (p=0,0001). Similarly, the median lateral-septal delay time value was 60 ms (10-120) before CRT and the median lateral-septal delay time value 6 months after CRT was 40 ms (10-65) (p=0.0001). The decrease lateral-septal delay time measurement value 6 months after CRT was statistically significant. The mean aortic preejection time of patients before CRT was 142.9±21.0 ms and the mean aortic preejection time 6 months after CRT was 122.1±21.2 ms (p=0.001). The decrease in aortic preejection time after CRT was statistically significant (Table 2).

Table 1. Distribution of demographic and clinical characteristics of the patients

Age (year)	63.3±10.5
Sex (Male/Female), n (%)	27 (53%) / 24 (47%)
Body mass index (kg/m^2)	29.5 ± 4.8
Hypertension, n (%)	30 (59%)
Coronary artery disease, n (%)	19 (37%)
Diabetes mellitus, n (%)	13 (26%)
Smoking, n (%)	34 (67%)
NYHA functional capacity (II/III/IV), n (%)	7 (14%) / 32 (63%) / 12 (23%)
Non-ischemic / ischemic ardiomyopathy, n (%)	30 (59%) / 21 (41%)
ACEi / ARB, n (%)	46 (90%)
Beta blocker, n (%)	46 (90%)
Loop diüretics, n (%)	46 (90%)
Spironolactone, n (%)	38 (75%)
Digoxin, n (%)	11 (22%)

NYHA: New York Heart Association, ACEi: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker.

Evaluation of Relationships Between Cardiologic Parameters and Laboratory Variables

When the relationships between cardiologic variables (echocardiographic parameters, ECG and 6-minute walking distance and parameters such as PICP, ICTP, PICP/ICTP ratio) are evaluated, no statistically significant relationships were found between these variables. A significant positive correlation was found be-tween pre-CRT PICP level and PICP/ICTP ratio (r=0.78; p=0.0001), a moderate positive correlation was found between post-CRT PICP level at 6 months and PICP/ICTP ratio (r=0.59; p=0.0001). A highly negative correlation was found between pre-CRT ICTP level and PICP/ICTP ratio (r=-0.67; p=0,0001), and a highly significant negative correlation was detected between ICTP level at 6 months after CRT and PICP/ICTP ratio at 6 months after CRT (r=-0.87; p=0.0001). While a weakly significant negative correlation was found between PICP levels 6 months before and after CRT and EF (r=-0.611; p=0.0001), positive correlation was detected between PICP level 6 months before and after CRT and basal SPWD pre and post-treatment. Significant negative correlation was found between PICP/ICTP ratio and EF at 6 months (r=-0.69; p=0.0001) (Table 3).

Table 2. Distribution of pre- and post-CRT measurements of patients

	Pre-treatment			Post-treatment			P value
	N	Mean±ss	Median (min-max)	N	Mean±ss	Median (min-max)	
6 min walk distance (meter)	51	255.8±83.8	238 (70-460)	40	334.2±82.7	335 (175-570)	**0.0001**
QRS period (msec)*	51	165.7±29.5	160 (100-280)	40	133.5±26.4	130 (80-200)	**0.0001**
PICP(µg/L)	51	560.2±300.4	475.9 (191.6-1200)	40	476.9±285.8	425.3 (134.4-1200)	**0.004**
ICTP(µg/L)	51	15.0±11.5	12.2 (1-40)	40	16.6±9.0	15 (3.7-40.0)	0.173
PICP /ICTIP ratio	51	79.7±10	46.8 (7.7-525.5)	40	37.1±32.8	28 (6.8-173.5)	**0.0001**
EF(%)*	51	28.9±4.2	30 (20-43)	40	34.8±7.3	35 (23-55)	**0.0001**
LVEDD(mm)*	51	66.5±8.3	67 (50-86)	40	62.6±8.4	60 (49-80)	**0.0001**
LVESD(mm)*	51	54.6±8.9	54 (38-71)	40	48.8±10.0	50 (24-70)	**0.0001**
SPWD (msec)	51	189.4±78.3	200 (13-320)	40	125.1±45.8	120 (40-250)	**0.0001**
IVMD (msec)	51	49.4±16.6	43 (10-87)	40	31.4±14.7	31 (5-68)	**0.0001**
Lateral-septal delay (msec)	51	60.3±17.2	60 (10-120)	40	39.5±16.0	40 (10-65)	**0.0001**
Aortic preejection time(msec)	26	142.9±21.0	142 (90-180)	15	122.1±21.2	120 (90-155)	**0.001**

PICP: Type I Collagen C-Terminal Propeptite, ICTP: Type I Collajen C-Terminal Telopeptite, EF: Ejection fraction, LVEDD: Left Ventricle End Diastolic Diameter, LVESD: Left Ventricle End Systolic Diameter, SPWD: Septal-to-posteriyor wall mechanical delay, IVMD: Interventricular mechanical delay, p*: dependent Group T testi; p: Wilcoxon test

Table 3. Correlation between PICP, ICTP levels and PICP/ICTP ration and other variables

		Initial PICP	Initial ICTP	Initial PICP/ICTP Ratio
Baseline 6 minute walk distance (meter)	r	0.26	0.05	0.27
	p	0.065	0.724	0.053
Baseline QRS period (msec)	r	0.09	0.13	0.17
	p	0.505	0.345	0.230
Baseline EF (%)	r	-0.37	-.15	-0.36
	p	**0.008**	0.287	**0.011**
Baseline LVEDD (mm)	r	-0.01	0.04	-0.01
	p	0.934	0.747	0.880
Baseline LVESD (mm)	r	-0.03	0.02	-0.01
	p	0.834	0.880	0.921
Baseline SPWD (msec)	r	**0.29**	0.08	0.10
	p	**0.039**	0.565	0.471
EF at 6 months (%)	r	-0.611	-0.36*	-0.69
	p	**0.0001**	**0.025**	**0.0001**
SPWD at 6 months (msec)	r	0.60	0.34*	0.48
	p	**0.0001**	**0.030**	**0.0001**
Baseline IVMD (msec)	r	0.20	-0.04	0.11
	p	0.151	0.803	0.436
Baseline lateral-septal delay (msec)	r	0.03	-0.06	0.17
	p	0.850	0.670	0.848
Baseline Aortic preejection time (msec)	r	0.22	0.11	0.17
	p	0.287	0.587	0.406

PICP: Type I Collagen C-Terminal Propeptite, ICTP: Type I Collajen C-Terminal Telopeptite, EF: Ejection fraction, LVEDD: Left Ventricle End Diastolic Diameter, LVESD: Left Ventricle End Systolic Diameter, SPWD: Septal-to-posteriyor wall mechanical delay, IVMD: Interventricular mechanical delay,

DISCUSSION

Correction of dyssynchrony, which is considered as one of the causes of myocardial fibrosis is aimed by CRT in heart failure, along with prevention of fibrosis development due to myocardial loading. In the con-text of collagen cycle in the development of myocardial fibrosis, which forms the basis of remodeling? Degradation products of propeptides enter the bloodstream. The collagen left after release of propep-tides, which has a structure of triple strand combine with other collagens to form collagen fibers. Small telopeptide is ICTP, which show the destruction of collagen type I (13). Cardiac fibrosis that occur as a re-sult of collagen cycle disorders that develop due to various causes is the main determinant of diastolic function and pumping capacity and prepare the basis for arrhythmias (14). After myocyte damage or ne-crosis that occurs due to various causes, these cause some changes (remodeling) in myocyte order and extracellular matrix structure. Cardiac remodeling starts months and even years before observation of symptoms of heart failure, and continues after development of symptoms.

As cardiac fibrosis has such important clinical consequences, the most critical point in treatment options may be considered as arresting and even reversing fibrosis. CRT is one of these treatment options. But although it is in use for a long time and there are studies on its effects on myocardial fibrosis, there is no general conclusion that it can regress myocardial fibrosis. There are also different opinions on the devel-opment of myocardial fibrosis. Most widely recognized opinion among these is increased collagen syn-thesis by fibroblasts and myofibroblasts, with simultaneous unchanged or decreased extracellular matrix collagen degradation (15). An opposite opinion is inhibition in collagen synthesis and/or increase in colla-gen degradation. PICP, which is among the markers that we evaluated, is mainly of cardiac origin. In a study by Querejeta et al, PICP was higher in hypertensive patients without heart failure than the control group. PICP levels of patients with heart failure were higher than both controls and hypertensive pa-tients. Also, endomyocardial biopsy was done in this study, and levels of PICP from peripheral blood and coronary sinus were compared with collagen fibril levels in tissue samples. A direct relationship was shown between these parameters (collagen fibril levels were high in those with high PICP levels)(16).

We investigated patients with NYHA II-IV heart failure in our study, and showed that serum PICP levels decrease 6 months after CRT implantation. Limitation of excessive cardiac collagen type I synthesis and accumulation is one of the mechanisms of action of CRT (17). Decrease instead of an increase in PICP lev-els with CRT in our study suggests that this may be the mechanism of action of the CRT. The hypothesis is that CRT decreases the mechanical stress on the left ventricle by improving left ventricular dyssynchrony. Thus stimulation of signal pathways in myocardial cells (protein kinase pathway activated by mitogen, etc) and thus decrease of collagen synthesis and release may be possible (18). The study by Querejeta et al on hypertensive patients is the first study demonstrating the direct relationship between PICP level and collagen tissue samples of cardiac biopsy, in which serum PICP level was found to be superior to echocar-diographic parameters in evaluating myocardial fibrosis and their results suggest that myocardial fibrosis may be assessed by measuring PICP levels only, without endomyocardial biopsy (19). On the basis of these results, use of PICP measurement may be considered a relatively low-cost non-invasive method in determining prognosis in patients with heart failure and evaluating the effects of treatment.

The other fibrosis marker that we have investigated, ICTP showed a stable level 6 months after CRT. This result suggests that CRT also has an effect on collagen degradation. ICTP is a degradation product of type I collagen and may be used as a marker of collagen type I degradation products. Klappacher et al have found increased ICTP levels in patients with dilated cardiomyopathy (20). Klappacher et al have shown a relationship between ICTP levels and myocardial collagen tissue. Stable levels of ICTP, which is a degrada-tion product, after CRT shows again that CRT is an effective treatment, as the increase in ICTP would be expected to continue due to the continuing progression of myocardial fibrosis in patients with heart fail-ure. But this increase may not have been observed in our study, due to a decrease in myocardial fibrosis with CRT.

In a study by Garc´ıa-Bolao et al in 2009, PICP / ICTP ratios were shown to decrease in patients responsive to CRT (21). The ratio of PICP of serum to evaluate collagen type I cycle and ICTP levels obtained in a simi-lar manner were suggested to be used as a strong predictor for patients responding to CRT. The PICP/ICTP ratio was found to be decreased 6 months after CRT in our study, and it was thought to have a relationship with EF. The mechanical characteristics of the heart change and EF and cardiac output in-crease with CRT. As in the study by Cleland et al, EF value showed a significant increase 6 months after CRT (22). In our study, a negative correlation between myocardial fibrosis markers PICP level and the PICP / ICTP ratio and EF was found, but it was weak. No relationship was detected between ICTP levels and EF. This may imply that an increase in EF increases cardiac output and myocardial perfusion and thus myocar-dial fibrosis is prevented. The increase in cardiac output by synchronized contractions of the left ventricle may be considered as one of the mechanisms preventing myocardial fibrosis.

When echocardiographic parameters are evaluated, LVESD measurement results were found to show a significant decrease 6 months after CRT. In the study by Stanciu et al, investigating anti-inflammatory and anti-remodeling relationships of CRT in patients with chronic heart failure, LVESD was shown to have de-creased (23). LVESD and

LVEDD showed a decrease 6 months after CRT in our study but we did not find any correlations with myocardial fibrosis markers. This may be due to the duration of follow-up.

LIMITATIONS

Our study has some important limitations. One of the most important limitations is the relatively small number of patients included in the study. Another important limitation is the follow-up duration of 6 months. Thus, long-term outcomes are not known. Biventricular pacing rate is not evaluated in patients after the procedure. Responder and non-responder were not fully compared. Left ventricular dyssyn-chrony is a three-dimensional and complex issue and selection of three-dimensional echocardiography for evaluation of these characteristics would be more appropriate. As generalized scar tissue, which is especially seen in ischemic patients may cause a decrease in clinical and echocardiographic response rates, the absence of magnetic resonance imaging to determine the location and size of scar tissue is an-other limitation of our study.

CONCLUSION

Our results show that CRT reduces the left ventricular dyssynchrony and consequently leads to positive changes in myocardial fibrosis markers. PICP level may be used as a marker in the determination of prog-nosis and follow-up of treatment of patients in future studies on a larger scale. Reducing the mechanical stresses on the left ventricle and returning of consequent remodeling may be one of the important mechanisms in the prevention of cardiac fibrosis.

Competing interests: The authors declare that they have no competing interest.

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Ethical approval: This study was approved by the Ethics Committee of Cukurova University with the protocol number of TTU-2015-4909.

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