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ORIGINAL ARTICLE

Impact of Cardiac Resynchronization Therapy on Indirect Inflammatory Markers

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Abstract

Background: Cardiac resynchronization therapy (CRT) is an established treatment for patients with symptomatic chronic heart failure with reduced ejection fraction (HFrEF) and prolonged QRS despite optimal pharmacological therapy. Inflammation plays a crucial role in the pathogenesis and progression of cardiovascular disease. The role of CRT pre-implantation inflammatory condition assessed using routine laboratory tests has been rarely investigated.

In this study we aimed to evaluate the effect of CRT on indirect inflammatory markers such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and lymphocyte-to- the monocyte (LMR) ratio.

Methods: 75 CRT patients were included in the study retrospectively. Before the CRT implantation, clinical and demographic data were recorded from all patients. NLR, PLR and LMR ratio were measured before CRT implantation. The patients were re-evaluated minimum six months after CRT; the above-mentioned parameters were measured again and compared to the pre-CRT period.

Results: Compared to the period before CRT, laboratory findings such as white blood cell (3.5 ± 2.2 103 uL vs. 3.2 ± 2.4 103 uL; p = 0.006), neutrophyl (1.9 ± 0.4 103 uL; vs. 1.4 ± 0.4 103 uL; p = 0.002), NLR (3.8 ± 0.3 103 uL; vs. 1.7 ± 0.1 103 uL; p <0.001), PLR (490.2 ± 199 103 uL; vs. 381 ± 105 103 uL; p < 0.001) levels were significantly lower after 6 months of CRT implantation. Lymphocyte counts (0.5 ± 0.3 103 uL vs. 0.8 ± 0.2 103 uL; p = 0.001) were significantly higher in the post CRT group. A significant and positive correlation of the reduction in NLR (rs = 0.362, p = 0.001) and PLR (rs = 0.562, p <0.001) was found with the increased six minute walking test (6-MWT).

Conclusion: The NLR, PLR and MLR were decreased after CRT implantation. The modest decrease in these parameters demonstrates the effect of restoring the heart's electromechanical synchrony after CRT on inflammation.

Key Words: Congestive Heart Failure, Cardiac Resynchronization Therapy, İnflammatory Markers.

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Introduction

Approximately 1–2% of the adult population in developed countries have heart failure (HF), with the prevalence rising to ≥10% among persons 70 years of age or older (1). HF can be classified into three types based on the condition of left ventricular (LV) systolic function: HF with preserved ejection fraction (EF) (EF≥ 50%), mid-range HF (EF:40 - 49 %) and HF with reduced ejection fraction (HFrEF) (EF< 40 %) (2) . Cardiac resynchronization therapy (CRT) is an established treatment for patients with symptomatic chronic HFrEF and prolonged QRS despite optimal pharmacological therapy.

By restoring the heart's electromechanical synchrony, CRT improves self-reported symptoms and reduces mortality and rehospitalization for heart failure (3). Unfortunately, almost a third of patients do not respond favourably to CRT (4). Several characteristics are associated with improved response, and thus survival following CRT implantation (5).

Inflammation plays a crucial role in the pathogenesis and progression of cardiovascular disease. Numerous inflammatory biomarkers are correlated with disease severity and prognosis across throughout HF (6). However, the role of CRT pre-implantation inflammatory condition assessed using routine laboratory tests has been rarely investigated.

In this study we aimed to evaluate the effect of CRT on indirect inflammatory markers such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and lymphocyte-to- the monocyte (LMR) ratio.

Materials and Methods

Study Population and Data Collection

Subjects consisted of 82 consecutive patients undergoing CRT, between January 2017 and December 2019, at Ondokuz Mayıs University School of Medicine Cardiology Department who were retrospectively enrolled into the study. Patients were included according to following criteria: (1) chronic HF with reduced LVEF (≤35%) and (2) prolonged QRS interval (≥130 msn) with LBBB morphology (3) have indication for CRT implantation according to the 2016 European Society of Cardiology guideline for the diagnosis and treatment of acute and chronic HF. CRT implantation was performed to all participants.

Patients with mechanical tricuspid valve, recent myocardial infarction or coronary artery bypass graft surgery (≤ six months), decompensated HF, malignancies, chronic inflammatory disease, haematological disorders, renal or hepatic disorders, right bundle branch block morphology on electrocardiogram (ECG), right ventricular pacing only, pacemaker upgraded to CRT, LV lead inserted into other than lateral or postero-lateral branches of coronary sinus, life expectancy of less than 12 months, and follow-up interval less than six months were excluded from the study. Thus, 7 patients were excluded, and the study cohort included a total of 75 patients. All patients included in the study with either sinus rhythm or atrial fibrillation provided biventricular pacing over 90%.

An independent physician who was blinded to all other data performed the clinical evaluation, including assessment of New York Heart Association (NYHA) class, in all of the patients. QRS duration was measured by surface ECG using the widest QRS complex from the II, V1, and V6 leads. All patients were evaluated in terms of age, gender, coronary artery disease history, diabetes mellitus, hyperlipidaemia, hypertension, and other concomitant diseases. Patients were classified as ischaemic or nonischaemic aetiology of HF. The patients underwent a detailed echocardiographic examination at baseline and six months after the CRT.

Echocardiography

Transthoracic echocardiography (TTE) was performed by an experienced echocardiography specialist who was blinded to other data. Vivid E9 (GE Vingmed Ultrasound, Horten, Norway) TTE device and M5S (1.5-4.5 MHz) ultrasound probe were used for the echocardiographic measurements. Left ventricular end-systolic volume (LVESV), left ventricular end-diastolic volume (LVEDV), left ventricle end-diastolic (LVEDD) and end-systolic diameters (LVESD), and left atrium (LA) anteroposterior diameter were measured from the long axis view of the heart using TTE. Ejection fraction (EF) was calculated by Modified Simpson method using apical 4-chamber and 2-chamber images. Valvular heart pathologies were detected and graded. Pulmonary arterial pressure was measured.

CRT implantation

Following left pectoral region incision, subclavian venous puncture was performed, and right ventricle and right

atrium leads were placed. After this, coronary sinus was found using a left amplatz catheter, and images were recorded using a contrast-enhancing agent for the selection of the suitable branch. LV lead was placed on the lateral or posterolateral branch of coronary sinus if possible. All electrodes were connected to the generator, and the pouch was closed following stimulus and threshold values were controlled**.** After implantation AV delay of the patients was set to be 120 ms, and VV delay was 0 ms for optimal resynchronization.

Laboratory measurements

In our hospital, blood samples were collected from the antecubital vein within 24 hours of hospital admission. Complete blood cell counts including total white blood cell (WBC), platelet, neutrophil, lymphocyte, and monocyte counts, and haemoglobin level were all measured with an autoanalyzer. NLR was calculated by dividing the neutrophil count by the lymphocyte count. PLR was calculated by dividing the platelet count by the lymphocyte count. LMR was calculated by dividing the lymphocyte count by the monocyte count. Venous blood samples were obtained without venostasis by venepuncture of the large antecubital veins of the patients at least 24 h before CRT implantation and were immediately studied in the laboratory without any time delay. Study patients were re-evaluated minimum 6 months after the CRT implantation and the parameters of pre-CRT and post-CRT periods were compared eachother.

Definitions

Ischemic cardiomyopathy and non-ischemic cardiomyopathy definitions were made based on the presence or absence of myocardial infarction events or 75% or more stenosis in the left coronary artery.

Statistical analysis

Statistical analyses were performed using SPSS 22 for Windows (SPSS Inc., Chicago, IL, USA). The continuous variables were tested for a normal distribution using the Kolmogorov–Smirnov test. Normality was checked using the Shapiro–Wilk statistic test. Normally distributed data were presented as the mean ± standard deviation and non-normally distributed data as the median with an interquartile range. The categorical variables were expressed as percentages. A paired sample t test or Wilcoxon's signed-rank test was performed according to the normality of the clinical variables to compare clinical parameters before and six mounth after the CRT. Spearman correlation analysis was used for variables not showing normal distribution. The NYHA class change was compared using Cochran Mantel-Haenszel test for ordered variables. Spearman correlation analysis was performed to examine the relationship between change in NLR, PLR and six-minute walking test (6-MWT). Statistical significance was set at $p < 0.05$.

Results

A total of 75 CRT patients were included in the study. Of the study patients, 54% were males; the mean age was 63.1 ± 12.5 years, and 64% had ischemic etiology. Hypertension was present in 80% of patients. Therapy with beta-blockers and diuretics were at high rates (85.3% vs 96%, respectively). The basic clinical features and laboratory parameters of the study groups are listed in **Table 1**. The echocardiogram and laboratory findings and the clinical parameters evaluated before CRT and after six months are shown in **Table 2**. The heart rate (72.9 ± 4.9 bpm vs 62.8 ± 6.5 bpm, p = 0.002). The LVESV, LVEDV, LVESD and LVEDD decreased significantly ($p < 0.05$). While significant increases occurred in LVEF (30.6 ± 2.9% vs 31.9 ± 2.5%, $p < 0.001$) and the cardiac index (2.3 ± 0.4 $L/min/m^2$ vs 2.5 ± 0.5 $L/min/ m^2$, $p < 0.001$), no significant changes were observed in the mitral regurgitation figure (**≥ moderate)** (31 vs 27, p = 0.288)**.** The patients exhibited significant NYHA classes improvement following the initiation of CRT. 6-MWT significantly increased after 6 months of CRT implantation (256 ± 42 vs. 296 ± 52; p=0.002. In their laboratory findings white blood cell (3.5 ± 2.2 10^3 uL vs. 3.2 ± 2.4 10^3 uL; p = 0.006), neutrophyl (1.9 ± 0.4 10^3 uL; vs. 1.4 ± 0.4 10^3 uL; p = 0.002), NLR (3.8 ± 0.3 10^3 uL; vs. 1.7 ± 0.1 10^3 uL; $p < 0.001$), PLR (490.2 ± 199 10^3 uL; vs. 381 ± 105 10^3 uL; $p < 0.001$) levels were significantly lower after 6 months of CRT implantation. Lymphocyte counts (0.5 ± 0.3 10^3 uL vs. 0.8 ± 0.2 10^3 uL; p = 0.001) were significantly higher in the post CRT group. In addition, there was no difference between the groups in terms of other laboratory findings and LMR ($p > 0.05$).

A significant and positive correlation of the reduction in NLR was found with the increased 6-MWT (rs = 0.362, p = 0.001) **(Fig.1A)**. A significant and positive correlation of the reduction in PLR was found with the increased 6-MWT (rs = 0.562, $p < 0.001$) **(Fig.1B)**.

Table 1. Baseline demographic and clinical parameters of the study population

Variable	(n=75)
Age (years)	63.1 ± 12.5
Gender	
Men, n (%)	41 (54.6)
Women, n (%)	34 (45.3)
Body mass index (kg/m²)	22.6 ± 2.6
Smoking	26 (34.6)
Etiology of heart failure	
Ischemic	48 (64)
Non-Ischemic	27 (49)
NYHA class, n (%)	
II	25 (33.3)
III	39 (52)
IV	11 (14.6)
Hypertension, n (%)	60 (80)
Diabetes mellitus, n (%)	28 (37.3)
Atrial fibrillation, n (%)	18 (24)
Beta-blocker, n (%)	64 (85)
ACEI or ARB, n	67 (89)
ARNI, n	5 (6)
Aldosterone receptor blocker, n (%)	51 (68)
Diuretic, n (%)	72 (96)
Ivabradine, n (%)	30 (40)
Digoxin, n (%)	16 (21)
ECG branch block	124.2 ± 9.1
LBBB, n	61 (81.4)
Other bransch blocks, n	14 (18.6)

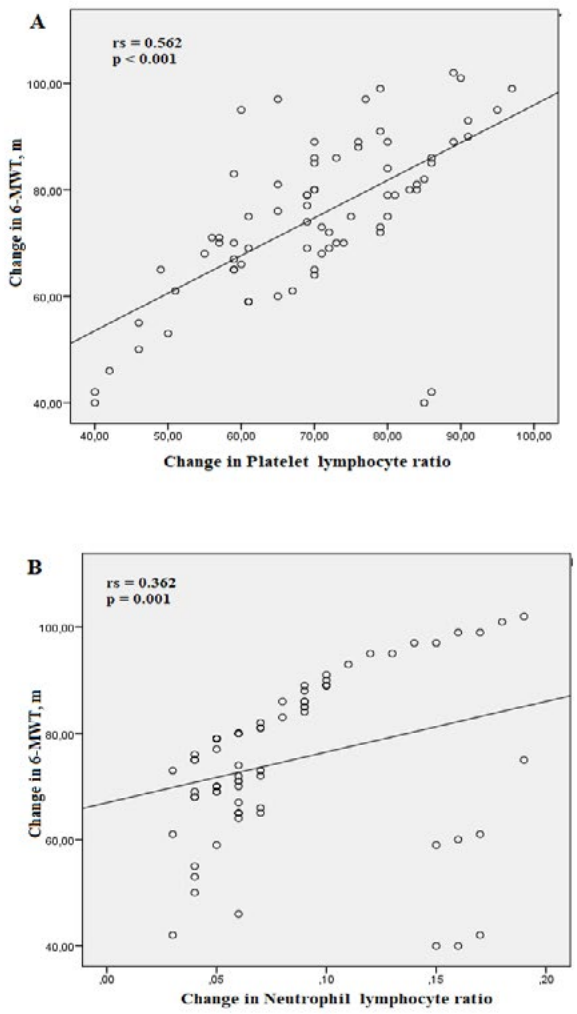
Numerical variables are presented as mean ± SD and categorical variables as percentages. NYHA: New York Heart Association; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; ECG: Electrocardiography; LBBB: Left Bundle Branch Block

Table 2. Echocardiographic, laboratory and clinical parameters before and six month after CRT

Parameters	Baseline	6rd month	p value
Heart rate (bpm)	72.9 ± 4.9	62.8 ± 6.5	0.002
QRS duration, msn			
Creatinine, mg/dL	1.01 ± 0.26	1.14 ± 0.28	0.098
Potassium, mEq/L	4.1 ± 0.2	4.4 ± 0.3	0.097
NYHA class			<0.001
I n,(%)	0	3 (4)	
II n,(%)	25 (33.3)	40 (53.3)	
III n,(%)	39 (52)	25 (33.3)	
IV n,(%)	11 (14.6)	7 (9)	
6-MWT, m	256 ± 42	296 ± 52	0.002
White blood cell, 10^3 uL	3.5 ± 2.2	3.2 ± 2.4	0.006
Hemoglobin, g/dL	10.4 ± 2.6	10.8 ± 2.4	0.058
Neutrophil, 10^3 uL	1.9 ± 0.4	1.4 ± 0.4	0.002
Lymphocyte, 10^3 uL	0.5 ± 0.3	0.8 ± 0.2	<0.001
Monocyte, 10^3 uL	0.6 ± 0.3	1 ± 0.2	<0.001
Platelet, 10^3 uL	245 ± 43	305 ± 53	<0.001
NLR	3.8 ± 0.3	1.7 ± 0.1	<0.001
PLR	490 ± 199	381 ± 105	<0.001
LMR	0.8 ± 0.25	0.8 ± 0.21	0.856
LVEDd, mm	58 (56-61)	56 (55-61)	0.017
LVESd, mm	44 (42-47)	41.5 (40-45)	<0.001
LVEF, (%)	30.6 ± 2.9	31.9 ± 2.5	<0.001
LVEDV, mL	161 (146-176)	153.5 (146-167)	0.007
LVESV, mL	114 (100-125)	100 (96-110)	<0.001
Cardiac Index (L/min/m²)	2.3 ± 0.4	2.5 ± 0.5	0.001
Mitral insufficiency (≥ moderate) n, (%)	31 (34)	27 (31.3)	0.288
sPAP, mmHg	33.9 ± 3.7	30.1 ± 2.9	<0.001

Numerical variables are presented as mean± SD and categorical variables as percentages. NYHA: New York Heart Association; 6-MWT: Six month walk test; NLR: neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; LMR: Lymphocyte-monocyte ratio; LV: Left ventricular; EF: 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; sPAB: Systolic pulmonary arterial pressure.

Fig.1 (A) Correlation of change in 6-MWT with PLR. (B) Correlation of change in 6-MWT with change in NLR. rs: indicates correlation coefficient.



Discussion

As a result of our study, we found that CRT causes a moderate decrease in indirect inflammatory parameters. These data suggest that decrease in inflammatory markers of which increased levels are associated with poor outcome in cardiovascular events, important in positive prognostic effects after CRT.

The prevalence of heart failure, especially with the decrease in deaths due to myocardial infarction and sudden cardiac death, is increasing worldwide (1). Endpoints have improved considerably with advances in HF treatment (2).

Cardiac resynchronization therapy, which has a significant contribution to the positive effects, increases cardiac performance in selected eligible patients and provides a significant reduction in symptoms and morbidity and mortality (3). In electrical and mechanical synchronization failure in HF patients, the right and LV leads placed with CRT create two ventricular activation waves that are distributed in opposite directions starting from where they are placed. The beneficial effect of these two depolarization waves is to synchronize the contraction of the LV walls. Thus, the performance of the myocardium, which starts to contract synchronously, increases with both the mechanical effect and the reversing remodelling effect (7).

Heart failure is a systemic condition with increased levels of inflammatory markers. Treatments targeting these pathways have shown a favourable prognostic effect in this syndrome (8).

It is known that the immune system and inflammation play an important role in the pathogenesis of HF. However, the effect of the immunological system on prognosis remains unclear (8). The basis of the interaction between leukocyte derivatives and HF is highly complex (9).

In summary, it has been suggested that systemic cytokine release, which potentially causes lymphocyte apoptosis and activation of the hypothalamic-pituitary-adrenal axis, causes a decrease in % lymphocyte count, especially due to physical stress (8). Previous studies have shown that % lymphocyte count is significantly associated with HF incidence, HF hospitalizations and mortality (10).

Neutrophils play an important role in the inflammation process by producing myeloperoxidase, which promotes phagocytic function. Increased levels of this enzyme also cause excessive free radical production, which has detrimental effects on the myocardium (11). In this context, Avcı and his friends observed a significant negative correlation between NLR and LVEF in patients with idiopathic dilated cardiomyopathy. They found worse functional classes in patients with higher NLR levels in their study and concluded that the higher NLR was useful for evaluating the severity of HF (11). Yıldız and her friends reported higher NLR levels and decreased functional capacity in HFrEF patients with similar LVEF (12). Additionally, Agacdiken and his friends found that the basal NLR is a predictor of the response to CRT (13). Balcı et al., in their study evaluating the response to CRT, found higher NLR and PLR values in patients who did not respond to CRT (14). In our study, a significant decrease in NLR, PLR and MLR was detected in all patient groups after CRT implantation. These results suggest that; the effectiveness of CRT can be demonstrated by using simple inflammatory markers.

This study has some limitations. First, this retrospective study was conducted in a single centre with a small sample size. Second, additional inflammation markers were not assessed to address the other confounding factors. Third the relationship between the inflammatory markers and clinical outcomes were not evaluated. A prospective randomized multi-center study with a larger study population might increase the significance of the presented results.

The NLR, PLR and MLR were decreased after CRT implantation. The modest decrease in these parameters demonstrates the effect of restoring the heart's electromechanical synchrony after CRT on inflamation. These results appeared to be associated with positive response to CRT.

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Declarations

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