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Neutrophil-to-lymphocyte ratio predicts response to cardiac resynchronization therapy

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Background: Neutrophil-to-lymphocyte (N/L) ratio has been associated with adverse outcomes in patients with acute coronary syndromes and increased risk for long-term mortality in patients with acute decompensated heart failure. We aimed to investigate the prognostic value of neutrophil-to-lymphocyte ratio on response to cardiac resynchronization therapy (CRT).

Material/Methods: Seventy consecutive patients (mean age 58±13 years; 40 men) undergoing CRT were included in the study. Hematological and echocardiographic parameters were measured before and 6 months after CRT. Echocardiographic response to CRT was defined as a ≥15% reduction in left ventricular end-systolic volume at 6-month follow-up.

Results: After 6 months of CRT, 49 (70%) patients were responders. After 6 months, left ventricular ejection fraction (LVEF) had significantly increased, from 21±7% to 34±11% in responder patients (p=0.001). N/L ratio decreased significantly, from 2.4±1 to 2.1±0.7 in responders (p=0.04). In multivariate analysis, significant associates of echocardiographic response to CRT was evaluated adjusting for age, etiology of cardiomyopathy, baseline LVEF, New York Heart Association functional class, C-reactive protein, and baseline N/L ratio. Baseline N/L ratio was the only predictor of response to CRT (OR 1.506, 95% CI, 1.011–2.243, p=0.035).

Conclusions: N/L ratio at baseline could help to identify patients with response to CRT.

Key words: cardiac resynchronization therapy • heart failure • neutrophil • lymphocyte

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Background

Cardiac resynchronization therapy (CRT) is a major treatment for selected patients with heart failure (HF). CRT has been demonstrated to improve HF symptoms, exercise capacity, and quality of life, and to reduce HF hospitalization rates and mortality [1,2].

Neutrophil-to-lymphocyte (N/L) ratio is a new prognostic marker in patients with CAD undergoing coronary angiography, percutaneous coronary intervention, and coronary artery bypass grafting [3,4]. Recently, higher N/L ratio has been associated with increased risk for mortality in patients with acute decompensated HF [5]. However, no data exist about the association between N/L ratio and response to CRT. We investigated the relationship between N/L ratio and response to CRT.

Material and Methods

Patients

Seventy consecutive patients (mean age 58±13 years; 40 men) undergoing CRT were included in the study. Patients were selected according to following criteria: (1) chronic heart failure (New York Heart Association functional class III or IV), (2) wide QRS interval (≥120 ms), and (3) left ventricular ejection fraction (LV EF) ≤35%. Patients with hematological disease, cancer, ongoing systemic inflammatory conditions, and autoimmune disease were excluded from the study. Sixty-six patients had left bundle branch block. The remaining 4 patients had right bundle branch block. Clinical evaluation included the assessment of NYHA functional class.

Written informed consent was obtained from all patients. The study was approved by the local ethics committee.

Cardiac resynchronization therapy device implantation

All pacemaker implantations were performed by left infraclavicular approach. Right atrial and ventricular leads were implanted using a transvenous approach. LV leads were inserted by a transvenous approach through the coronary sinus into a cardiac vein of the free wall. Patients received a biventricular pacemaker (InSync III, Medtronic Inc, Minneapolis, Minnesota) or a biventricular cardioverter-defibrillator (InSync ICD, Medtronic Inc, Minneapolis, Minnesota). The atrioventricular interval was optimized using Doppler echocardiography after 1 week of implantation.

Echocardiography

Patients were imaged in the left lateral decubitus position with a commercially available system (VIVID 7, General Electric-Vingmed Ultrasound, Horten, Norway). Images were obtained with a 2.5-MHz broadband transducer at a depth of 16 cm in the parasternal and apical views (standard long-axis, 2- and 4-chamber images). Standard 2-dimensional and color Doppler data triggered to the QRS complex were saved in cine-loop format. LV volumes were calculated using the Teicholz method and LVEF was calculated from the conventional apical 2- and 4-chamber images using the biplane Simpson's technique [6]. All echocardiographic measurements after CRT implantation were made with the device in active pacing mode. Transthoracic echocardiography was performed 1 week before pacemaker implantation and repeated 6 months later. Echocardiographic response to CRT was defined by a ≥15% reduction in left ventricular end-systolic volume at 6-month follow-up [7].

Blood samples

Fasting blood samples were drawn from a large antecubital vein at admission. The samples were centrifuged for 10 min and blood counts were measured by using Cell-Dyn 3700 (Abbott, IL, USA) at baseline and 6 months later. Serum C-reactive protein (CRP) levels were measured by a fluorescent polarization immunoassay (Abbott Diagnostics, Abbott Park, Illinois).

Statistical analysis

All analyses were performed with the statistical software program SPSS V.13.0. Continuous data are expressed as mean ±standard deviation (SD). The Mann-Whitney U test was used to assess differences in baseline clinical, echocardiographic, and hematological parameters between responder and non-responder patients. A comparison of the clinical, hematological and echocardiographic variables before and after CRT was performed by paired sample t-test or Wilcoxon signed-rank test. Variables associated with CRT response in univariate analysis were entered into a forward stepwise logistic regression model. A value of $p<0.05$ was considered statistically significant.

Results

The study population consisted of 70 patients. Baseline characteristics of the study group are shown in Table 1. Medication included angiotensin-converting enzyme inhibitors in 91%, beta-blockers in 89%, and diuretics in 90%. All medication was continued after CRT implantation. After 6 months of CRT, 49 (70%) patients were responders. The baseline clinical, hematological and echocardiographic parameters for responders and non-responders showed no statistically significant differences (Table 2).

After 6 months, LVEF had significantly increased from 21±7% to 34±11% in responders ($p=0.001$). There was no significant

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Table 1. Patient characteristics (n=70).

Age (years)	58±13
Men (n/%)	40/57%
Etiology	
Nonischemic (n/%)	44/63%
Ischemic (n/%)	26/37%
Hypertension (n/%)	43/61%
Diabetes (n/%)	16/23%
AF (n/%)	10/14%
Use of ACE-inhibitors or ARB (n/%)	64/91%
Use of beta-blocker (n/%)	62/89%
Use of diuretic (n/%)	63/90%
NYHA (mean)	3.0±0.5
LV EF (%)	22±7

AF – atrial fibrillation; ACE – angiotensin converting enzyme; ARB – angiotensin receptor blocker; NYHA – New York Heart Association; LV EF – left ventricular ejection fraction.

increase in LVEF in non-responders at 6-month follow-up (21±6% *vs.* 24±6%, p=0.06). Mean NYHA functional class in responders and non-responders were 3.1±0.6 and 3.2±0.5, respectively (p=0.62). At 6 months, mean NYHA functional class improved from 3.1±0.6 to 2.1±0.3 in responders (p=0.001). There was no significant change in mean NYHA functional class in non-responders (3.2±0.5 *vs.* 3±0.2, p=0.26). N/L ratio was decreased significantly, from 2.4±1 to 2.0±0.7 in responder patients (p=0.03). However, N/L ratio was increased from 3±1.7 to 3.6±1.5 in non-responder patients (p=0.37) (Table 3). CRP was decreased significantly, from 0.54±0.36 to 0.39±0.28 in responder patients (p=0.001). CRP increased significantly, from 0.74±0.42 to 1.05±0.52 in non-responder patients (p=0.006)

In multivariate analysis, significant associates of echocardiographic response to CRT were evaluated adjusting for age, etiology of cardiomyopathy, baseline LVEF, NYHA functional class, CRP, and baseline N/L ratio. Baseline N/L ratio was the only predictor of response to CRT (OR 1.506, 95% CI, 1.011–2.243, p=0.035).

Discussion

Cardiac resynchronization therapy is considered an important treatment option of patients with wide QRS and advanced

Table 2. Baseline clinical, echocardiographic and haematological parameters of responder and non-responder patients.

	Responders (n=49)	Non-responders (n=21)	p
NYHA (mean)	3.1±0.6	3.2±0.5	p=0.62
LVEDD (mm)	68±8	70±11	p=0.37
LVESD (mm)	56±12	59±13	p=0.34
LAD (mm)	43±7	46±7	p=0.29
LVEF (%)	21±7	21±6	p=0.52
RVD (mm)	25±3	25±5	p=0.74
LVEDV (mL)	233±80	251±99	p=0.28
LVESV (mL)	159±60	170±83	p=0.55
Neutrophil ($\times 10^9$/L)	4.5±1.3	4.3±0.9	p=0.87
Lymphocyte ($\times 10^9$/L)	2.1±0.7	1.8±0.7	p=0.06
N/L ratio	2.37±1	3.0±1.7	p=0.20
CRP	0.54±0.36	0.74±0.42	p=0.06

NYHA – New York Heart Association; LVEDD – left ventricular end-diastolic diameter; LVESD – left ventricular end-systolic diameter; LAD – left atrium diameter; LVEF – left ventricular ejection fraction; RVD – right ventricular diameter; LVEDV – left ventricular end diastolic volume; LVESV – left ventricular end systolic volume; N/L – neutrophil to lymphocyte; CRP – C-reactive protein.

CHF who are receiving optimal medical treatment. However, prediction of response to CRT remains problematic and an important proportion of patients do not respond to CRT, although they are selected according to current patient selection criteria [8–10].

Additional echocardiographic, electrocardiographic, and blood markers have been investigated in various studies to find patients most likely to respond CRT [11–14]. To the best of our knowledge, our study is the first to investigate the prognostic significance of N/L ratio in HF patients who underwent CRT.

Lymphocytopenia has been independently associated with increased mortality in patients with acute and chronic HF [5,15]. Downregulation of the proliferation and differentiation of lymphocytes, neurohumoral activation, and lymphocyte apoptosis have been suggested as potential mechanisms for lymphocytopenia [5]. In our study, lymphocyte count was lower in the non-responder patient group. Although the difference in lymphocyte count between responder and non-responder patients was not significant, low lymphocyte count in non-responder patients may reflect a more advanced disease stage.

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Table 3. Comparison of baseline and 6 months of clinical, echocardiographic and hematologic measuments in responder and non-responder patients.

	Responders (n=49)			Non-responders (n=21)		
	Baseline	6 months	P value	Baseline	6 months	P value
NYHA (mean)	3.1±0.6	2.1±0.3	0.001	3.2±0.5	3±0.2	0.26
LVEDD (mm)	68±8	61±9	0.001	71±12	69±12	0.13
LVESD (mm)	56±12	48±12	0.07	59±13	58±12	0.10
LVEF (%)	21±7	34±11	0.001	21±6	24±6	0.06
LA (mm)	43±7	42±5	0.23	46±7	45±7	0.06
RV (mm)	25±3	23±3	0.003	25±5	26±5	0.07
LVEDV (mL)	233±80	186±69	0.001	251±99	238±96	0.09
LVESV (mL)	159±60	111±54	0.001	170±83	166±87	0.06
Neutrophil ($\times 10^9$/L)	4.5±1.3	4.3±1.2	0.25	4.3±0.9	5.5±2.1	0.31
Lymphocyte ($\times 10^9$/L)	2.1±0.7	2.3±0.7	0.32	1.8±0.7	1.7±0.8	0.95
N/L ratio	2.4±1	2.0±0.7	0.03	3±1.7	3.6±1.5	0.37
CRP	0.54±0.36	0.39±0.28	0.001	0.74±0.42	1.05±0.52	0.006

NYHA – New York Heart Association; LVEDD – left ventricular end-diastolic diameter; LVESD – left ventricular end-systolic diameter; LVEF – left ventricular ejection fraction; LA – left atrium; RV – right ventricle; LVEDV – left ventricular end-diastolic volume; LVESV – left ventricular end-systolic volume; N/L ratio – neutrophil to lymphocyte ratio; CRP – C-reactive protein.

In addition, lymphocyte and neutrophil counts were not significantly changed in responder and non-responder patient groups. However, lymphocyte count was increased and N/L ratio was significantly decreased in responder patients.

CRP is a pentameric protein associated with inflammation, and elevated CRP levels have been observed in HF patients [16]. Also, higher CRP levels were associated with advanced HF and independently with mortality and morbidity [17]. Antiinflammatory effects of CRT have been demonstrated [18,19]. In our study, baseline CRP levels were not statistically different, but CRP levels were significantly reduced in responder patients in contrast to non-responder patients. The increased lymphocyte count, decreased N/L ratio, and decreased CRP in responder patients may reflect decreased systemic inflammation with CRT response, which in turn may help in development of reverse remodelling.

In addition, the importance of baseline cardiac dimensions in prognosis and response to CRT has been reported previously [20–22]. The mean left ventricular end-diastolic diameter (LVEDD) in responder patients was larger than in non-responder patients. Although the difference was not statistically significant, increased mean LVEDD in non-responder patients may also relate to a more progressive disease and extensive scar tissue.

Our study was limited in that it was a single-center, nonrandomized design and the study sample was small; a larger study population might increase the significance of the presented data.

Conclusions

Our data suggest that determination of N/L ratio at baseline could help identify patients with response to CRT.

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