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Correlation of Inflammation, Lipidogram and Clinical Readings in Chronic Heart Failure Patients †

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Abstract: *Background and Objectives:* While myocardial damage in heart failure (HF) patients with reduced ejection fraction (HFrEF) has been shown to be driven by oxidative stress, inflammation is a recognized factor in disease progression in both HFrEF and HF with preserved ejection fraction (HFpEF). Inflammation is presented as regulated by platelet-induced activation of blood leukocytes. Neutrophils take part in maintaining of pro-inflammatory state in HF. Hypercholesterolemia is stated to heighten neutrophil production, which contributes to accelerated cardiovascular inflammation. HF pathogenesis differences in the different HF phenotypes remain to be investigated. Aim: to determine differences in complete blood count, C-reactive protein (CRP) concentration, lipidogram and clinical readings between chronic HF (CHF) without previous myocardial infarction (MI) groups according to EF and between HFrEF groups according to MI presence in CHF development history and correlations between these readings. *Materials and Methods*: Four groups of patients (n = 266) were analyzed. 208 patients diagnosed with CHF who had had no documented history of previous MI were separated into two groups according to left ventricular ejection fraction (LVEF): LVEF ≥ 50%, n = 117; LVEF < 50%, n = 91. Additionally, 149 HFrEF patients were separated into two additional groups: those who had had no MI (n = 91) and those with MI (n = 58). Laboratory and clinical readings were taken from the patients' medical histories. *Results*: MCHC was lower and RDW-CV was higher in the lower EF group without a history of MI (337.32 (10.60) and 331.46 (13.13), p=0.004; 13.6 (11.5-16.9) and 14.7 (12.6-19.1), p=0.001). Lymphocyte percentage and lymphocyte-to-monocyte ratio (LYM/MON) were lower in the lower EF group without a history of MI (30.48 (10.87), 26.98 (9.08), p=0.045; 3.33 (1.22-9.33), 3 (0.44-6.5), p=0.011). CRP concentration (6.9 (1.46-62.97), 7 (1-33.99), p=0.012) was higher in HFrEF with MI in comparison with the group without MI. Neutrophil count correlated with PLT (r_s=0.278, p=0.001) and weight (r_p=0.196, p=0.024). Lymphocyte count correlated with PLT and RDW-CV (r_s=0.200, p=0.018; r_s=-0.223; p=0.032) and body mass index (r_p=0.186, p=0.032). RDW-CV and monocyte count correlated with NT-proBNP and serum creatinine (r_s=0.358, p=0.034; r_s=0.424, p<0.001 and r_s=0.354, p=0.012; r_s=0.205, p=0.018 respectively). Total cholesterol concentration correlated with LYM/MON, monocyte percentage, lymphocyte percentage and count (r_s=0.534, p<0.001; r_s=-0.312, p=0.029; r_s=0.355, p=0.012; r_s=0.397, p=0.004 respectively). EF correlated with MCHC and RDW-CV (r_s=0.273, p=0.001; r_s=-0.404, p<0.001). Total cholesterol concentration correlated with LYM/MON (r_s=0.534, p<0.001). HDL cholesterol concentration was lower in the HFrEF with MI group (0.96 (0.44-2.2); 0.92 (0.56-1.97, p=0.010). Uric acid concentration correlated with platelet-to-lymphocyte and lymphocyte-to-monocyte ratio (r_s=0.321, p=0.032; r_s=-0.341, p=0.023). Creatinine concentration correlated with monocyte percentage and count (r_p=0.312, p=0.001; r_p=0.287, p=0.003). *Conclusion:* 1) MCHC and lymphocyte percentage were lower and RDW-CV was higher in the HFrEF group without MI; CRP concentration was higher in HFrEF with MI in comparison with the group without MI; 2) HDL cholesterol concentration was lower and CRP concentration was higher in the HFrEF group with MI in comparison with the group without MI; total cholesterol concentration correlated with

LYM/MON; 3) monocyte, lymphocyte count and their ratio correlated with patients' condition reflected readings NT-proBNP, serum creatinine, uric acid concentrations.

Keywords: chronic heart failure; pro-inflammatory state; HFpEF; HFrEF; cholesterol, monocyte, lymphocyte, lymphocyte-to-monocyte ratio

1. Introduction

In the traditional model of heart failure (HF) pathophysiology, HF with reduced ejection fraction (HFrEF) has been mainly attributed to ischemic left ventricular (LV) remodeling [1–3], whereas HF with preserved ejection fraction (HFpEF) has been attributed to hypertension [4–7]. While myocardial damage in HFrEF has been shown to be driven by oxidative stress, inflammation is a recognized factor in disease progression in both HFrEF and HFpEF [8–10]. The latest researches have been showing recognition to a novel paradigm of chronic HF (CHF) pathogenesis [5,9,11–14]. Consequently, metabolism-related concomitant diseases (overweight/obesity, diabetes mellitus, dyslipidemia) are considered to play a crucial role in systemic pro-inflammatory condition maintenance in HFpEF [15,16].

Inflammatory processes are presented as regulated by platelet-induced activation of blood leukocytes. Neutrophils take part in maintaining a pro-inflammatory state in the pathophysiology of HF [17]. Hypercholesterolemia is stated to heighten neutrophil production, which contributes to accelerated cardiovascular inflammation [16]. Therefore, researchers are attempting to identificate inexpensive, reliable and most importantly, rapid prognostic markers of HF. In recent years, a few studies have been conducted to investigate the complete blood count components and features and find easily applicable markers in everyday clinical practice [18–22].

While the underlying pathophysiological mechanism leading to HFpEF remains not entirely explicit, HF pathogenesis differences in different HF phenotypes remain to be investigated. Hence, we aimed to determine differences in complete blood count, C-reactive protein (CRP) concentration, lipidogram and clinical readings between different HF phenotypes and to find correlations between these readings.

2. Materials and Methods

Four groups of patients were analyzed (n = 266). The data from January 1, 2018 to February 1, 2021 were collected from the Hospital of Lithuanian University of Health Sciences Kauno klinikos Cardiology department and evaluated retrospectively. 208 patients diagnosed with CHF who had had no documented history of previous myocardial infarction (MI) were divided into two groups according to left ventricular ejection fraction (LVEF): LVEF ≥ 50%, n = 117 and LVEF < 50%, n = 91. Additionally, 149 HFrEF patients were separated into two additional groups: those who had had no documented history of previous MI (n = 91) and those with MI (n = 58). Laboratory and clinical readings were taken from the patients' medical histories. Exclusion criteria were malignancies, chronic obstructive pulmonary disease, bronchial asthma, autoimmune diseases, stage 4–5 chronic kidney disease (CKD, with eGFR < 30 ml/min/1.73^2), acute infections, i.e., common chronic or acute systemic inflammation supporting conditions. All of the investigations were approved and conducted in accordance with the guidelines of the local Bioethics Committee and adhered to the principles of the Declaration of Helsinki and Title 45, U.S. Code of Federal Regulations, Part 46, Protection of Human Subjects (revised 15 January 2009, effective 14 July 2009). The study was approved by the Regional Bioethics Committee at the Lithuanian University of Health Sciences (No. BE-2-2, 12 February 2020).

Microsoft Office Excel and IBM SPSS Statistics version 25.0 were used for data analysis. The normality of data was assessed with the Kolmogorov–Smirnov Test. Groups were compared by Independent Samples T-Test. For nonparametric statistics, a Mann–Whitney U-Test was performed for comparison between the groups. Pearson's correlation (r_P) analysis was performed when two variables were normally distributed; otherwise, Spearman's correlation (r_s) analysis was used. A p-value less than 0.05 was considered statistically significant.

3. Results

MCHC was lower and RDW-CV was higher in the lower EF group without a history of MI (337.32 (10.60) and 331.46 (13.13), p=0.004; 13.6 (11.5-16.9) and 14.7 (12.6-19.1), p=0.001) (Table 1).

Table 1. Total blood cell count readings in the groups according to LVEF in patients without MI.

Laboratory findings	LVEF ≥ 50 %, n = 117	LVEF < 50 %, n = 91	p-value
RBC, 10^{12}/l	4.59 (0.57)	4.61 (0.65)	0.791
HGB, g/l	137 (87-165)	136 (77-183)	0.477
MCHC, g/l	337.32 (10.60)	331.46 (13.13)	**0.004***
PLT, 10^9/l	202 (73-326)	204.5 (113-1097)	0.053
RDW-CV, %	13.6 (11.5-16.9)	14.7 (12.6-19.1)	**0.001***

LVEF – left ventricular ejection fraction, MI – myocardial infarction, RBC – red blood cells, HGB – hemoglobin concentration, MCHC – mean corpuscular hemoglobin concentration, PLT – platelets, RDW-CV – red cell distribution width. * Statistically significant values ($p < 0.05$).

Also, lymphocyte percentage and lymphocyte-to-monocyte ratio (LYM/MON) were lower in the lower EF group without MI (30.48 (10.87), 26.98 (9.08), p=0.045; 3.33 (1.22-9.33), 3 (0.44-6.5), p=0.011). CRP concentration between these groups did not differ (4.92 (6.21), 7.51 (12.29), p=0.099). (Table 2).

Table 2. Blood cell count, its ratio and CRP concentration readings in groups according to LVEF in patients without MI.

Laboratory findings	LVEF ≥ 50 %, n = 117	LVEF < 50 %, n = 91	p-value
NEU, %	58.20 (12.40)	61.12 (10.40)	0.137
NEU, 10^9/l	4.00 (1.42-15.53)	4.05 (1.47-9.61)	0.434
LYM, %	30.48 (10.87)	26.98 (9.08)	**0.045***
LYM, 10^9/l	1.98 (0.72)	1.78 (0.59)	0.071
MON, %	9.1 (4.7-13.7)	9.4 (3.2-15.9)	0.101
MON, 10^9/l	8.78 (2.69)	9.52 (2.81)	0.121
LYM/MON	3.33 (1.22-9.33)	3 (0.44-6.5)	**0.011***
CRP, mg/l	4.92 (6.21)	7.51 (12.29)	0.099

LVEF – left ventricular ejection fraction, MI – myocardial infarction, NEU – neutrophils, LYM – lymphocytes, MON – monocytes, LYM/MON – lymphocyte-to-monocyte ratio, CRP – C-reactive protein concentration. * Statistically significant values ($p < 0.05$).

Only hemoglobin concentration was significantly higher in the HFrEF group with a history of MI (136 (77–183), 131.5 (98–148), p=0.010) compared to the HFrEF group without MI. Other findings of complete blood count and lipidogram readings did not differ between these groups. Total cholesterol concentration (4.35 (2.46–7.10), 3.9 (2.72–6.71), p=0.016) and high-density lipoprotein concentration (0.96 (0.44–2.2), 0.92 (0.56–1.97), p=0.010) were lower, and CRP concentration (6.9 (1.46-62.97), 7 (1-33.99), p=0.012) was higher in HFrEF with MI in comparison with the group without MI (Table 3).

Table 3. Lipid profile and CRP concentration in HFrEF with and without MI.

Laboratory findings	LVEF < 50 % without MI, n = 91	LVEF < 50 % with MI, n = 58	p-value
Total cholesterol, g/l	4.35 (2.46-7.10)	3.9 (2.72-6.71)	**0.016***
LDL, g/l	2.97 (1.53-5.5)	2.52 (1.36-4.42)	0.101
HDL, g/l	0.96 (0.44-2.2)	0.92 (0.56-1.97)	**0.010***
TG, g/l	1.25 (0.39-3.28)	1.24 (0.51-6.78)	0.672
AC	3.55 (1.23-6.06)	3.25 (1.21-6.39)	0.591
CRP, mg/l	6.9 (1.46-62.97)	7 (1-33.99)	**0.012***

LVEF – left ventricular ejection fraction, MI – myocardial infarction, LDL – low-density lipoprotein concentration, HDL – high-density lipoprotein concentration, TG – triglyceride concentration, AC – atherogenic coefficient, CRP – C-reactive protein concentration. * Statistically significant values ($p < 0.05$).

Following correlations in the groups according to LVEF (HFrEF and HFpEF) in patients without MI were found. Neutrophil count correlated with PLT (r_s=0.278; p=0.001) and weight (r_p=0.196; p=0.024). Lymphocyte count correlated with PLT and RDW-CV (r_s=0.200; p=0.018; r_s=-0.223; p=0.032) and body mass index (r_p=0.186; p=0.032). RDW-CV and monocyte count correlated with NT-proBNP and serum creatinine (r_s=0.358; p=0.034; r_s=0.424; p<0.001 and r_s=0.354; p=0.012; r_s=0.205; p=0.018 respectively).

The different correlations were found in the HFrEF groups according to MI presence in the disease history. PLT correlated with neutrophil and lymphocyte count (r_s=0.328; p<0.001 and r_s=0.295; p=0.002). PLT/LYM and LYM/MON correlated with uric acid concentration (r_s=0.321; p=0.032 and r_s=-0.341; p=0.023). Creatinine concentration correlated with RDW-CV and monocyte percentage and count (r_p=0.302; p=0.012 and r_p=0.312; p=0.001 and r_p=0.287; p=0.003). Total cholesterol concentration correlated with LYM/MON, monocyte percentage, lymphocyte percentage and count (r_s=0.534, p<0.001; r_s=-0.312, p=0.029; r_s=0.355, p=0.012; r_s=0.397, p=0.004 respectively). LDL cholesterol concentration correlated with lymphocyte count and LYM/MON (r_s=0.320; p=0.018 and r_s= 0.388; p=0.005). HDL cholesterol concentration reversebly correlated with monocyte count (r_p=-0.236; p=0.035). Triglyceride concentration correlated with platelet and lymphocyte count (r_s=0.259; p=0.028 and r_s=0.292; p=0.034). LVEF correlated with MCHC and RDW-CV (r_s=0.273, p=0.001; r_s=-0.404, p<0.001). Additionally, a correlation between CRP concentration and MCHC (r_s=0.262, p=0.008) was observed, but no significant relationship between CRP concentration and lipid profile readings was found.

4. Conclusion

MCHC and lymphocyte percentage were lower and RDW-CV was higher in the HFrEF group without etiology of MI and correlated with LVEF. Thereby, relative hypochromia in patients with CHF is slightly associated with LV diastolic dysfunction. In addition, the development of anisocytosis is considered to share the same pathogenetic mechanisms with HF. For this reason, RDW can be regarded as a reliable marker of impaired systolic function. Lipidogram readings in the group without etiology of MI correlated with LYM/MON. Although a correlation between CRP and lipid profile was not found (possibly due to its lack of sensitivity to the low inflammatory environment), it should be clarified as a possible relationship between the low inflammation environment and lipid metabolism.

CRP was higher and HDL cholesterol concentration was lower in the HFrEF group with MI in disease history. Monocyte count and present reversible correlated with HDL cholesterol concentration in HFrEF group. Lymphocyte count correlated with total, LDL cholesterol and triglyceride concentrations.

Monocyte, lymphocyte count and their ratio correlated with patients' condition reflected readings NT-proBNP, serum creatinine, uric acid concentrations in all the groups.

Summarizing complete blood count readings lymphocyte and monocyte count indicating inflammation could be related to low inflammatory and lipid metabolism in CHF patients. It seems in HFrEF with MI in disease history inflammation environment could be higher in comparison with those without MI.

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