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Proceeding Paper

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

Greta Gujytė [1,*], Aušra Mongirdienė [1] and Jolanta Laukaitienė [2]

[1] Department of Biochemistry, Medical Academy, Lithuanian University of Health Sciences, Eiveniu Str. 4, LT-50103 Kaunas, Lithuania; ausra.mongirdiene@lsmuni.lt
[2] Cardiology Clinic, University Hospital, Lithuanian University of Health Sciences, Eiveniu Str. 2, LT-50161 Kaunas, Lithuania; jolanta_laukaitiene@yahoo.co.uk
* Correspondence: gujyte.greta@gmail.com
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Abstract: *Background and Objectives*: Inflammation is a recognized factor in disease progression in both heart failure (HF) patients with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF). Neutrophils take part in maintaining the 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 are yet to be investigated. Aim: To determine differences in complete blood count, C-reactive protein (CRP) concentration and lipidogram between chronic HF patients with an absence/presence of myocardial infarction (MI) history and preserved/reduced EF. *Materials and Methods:* We separated the patients (n = 266) according to chronic HF phenotype: (1) HFrEF patients (n = 149) into groups according to presence of MI: those who had had no MI (n = 91) and those with MI (n = 58); (2) chronic HF without MI according to left ventricular ejection fraction (LVEF): LVEF $\geq$ 50%, n = 117; LVEF < 50%, n = 91. Laboratory and clinical readings (age, weight, pulse, blood pressure, and body mass index (BMI)) were taken from the patients' medical histories. *Results*: Mean corpuscular hemoglobin concentration (MCHC) was lower and red cell distribution width—coefficient of variation (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). In the group according to LVEF without MI neutrophil count positively correlated with weight (r_p = 0.196, p = 0.024); lymphocyte count correlated with RDW-CV (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). CRP concentration (6.9 (1.46–62.97), 7 (1–33.99), p = 0.012) was higher and HDL concentration was lower (0.96 (0.44–2.2), 0.92 (0.56–1.97), p = 0.010) in HFrEF with MI in comparison with the group without MI. LVEF correlated with MCHC and RDW-CV (r_s = 0.273, p = 0.001; r_s = −0.404, p < 0.001). HDL cholesterol concentration was lower (0.96 (0.44–2.2); 0.92 (0.56–1.97, p = 0.010) and CRP concentration (6.9 (1.46–62.97), 7 (1–33.99), p = 0.012) was higher in the HFrEF with MI group. Uric acid concentration correlated with platelet-to-lymphocyte ratio and LYM/MON (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). A correlation between CRP and MCHC (r_s = 0.262, p = 0.008) was observed. *Conclusions*: Our findings revealed the higher pro-inflammatory condition in HFrEF group without MI in comparison with HFpEF without MI. LYM/MON can be appropriate as additional reading for evaluation of functional condition in HFrEF group without MI. It seems inflammation environment could be higher in HFrEF with MI in disease history in comparison with those without MI. HDL concentration inversely correlated with monocyte count and the percentages could show the relationship between the low-grade inflammation and lipid metabolism in HFrEF. Both MCHC and RDW-CV may be relevant in assessing the chronic HF patients' condition.

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1. Introduction

In the traditional model of heart failure (HF) pathophysiology, HF with reduced ejection fraction (HFrEF) has been related to ischemic left ventricular (LV) remodeling after myocardial infarction (MI) [1–3], whereas HF with preserved ejection fraction (HFpEF) has been attributed to chronic 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 studies have been showing recognition of a novel paradigm of chronic HF 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 [9,15].

Inflammatory processes are presented as regulated by cytokine-induced activation of blood leukocytes. Neutrophils take part in maintaining a pro-inflammatory state in the pathophysiology of HF [16,17]. Hypercholesterolemia is stated to heighten neutrophil production, which contributes to accelerated cardiovascular inflammation [9]. Monocytes are presented to be involved in inflammatory reactions in the heart as well [18]. Therefore, researchers are attempting to identify 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 [19–23].

While the underlying pathophysiological mechanism leading to HFpEF remains not entirely explicit, HF pathogenesis differences in different HF phenotypes (HFrEF and HFpEF) remain to be investigated. It is known that HFpEF can change to HFrEF. Additionally, chronic HF without MI history can be with reduced or preserved left ventricle ejection fraction (LVEF), and HFrEF can be after MI or without MI history. Hence, we aimed to determine differences in complete blood count, CRP concentration, lipidogram, and other hematological readings between different HF phenotypes and to find correlations between these readings. We think that a more accurate knowledge about the differences in chronic HF phenotypes could help the search for laboratory readings for improving a rapid and cheap diagnostic marker.

2. Materials and Methods

Four groups of patients were analyzed (n = 266). The data from 1 January 2018 to 1 February 2021 were collected from the Hospital of Lithuanian University of Health Sciences Kauno klinikos Cardiology department and evaluated retrospectively. We separated the patients according to chronic HF phenotype: (1) HFrEF patients into groups according to presence of MI, and (2) chronic HF without MI according to EF. 208 patients diagnosed with chronic HF who had had no documented history of previous MI were divided into two groups according to LVEF: LVEF $\geq$ 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 (age, weight, pulse, blood pressure, and body mass index (BMI)) 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), and 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

Mean corpuscular hemoglobin concentration (MCHC) was lower and red cell distribution width-coefficient of variation (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-coefficient of variation. * Statistically significant values ($p < 0.05$).

Additionally, 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 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 ($p < 0.05$).

The 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 reversibly 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. Discussion

Both post-ischemic necrosis (a reason of HFrEF) and obesity or chronic hypertension (a reason of HFpEF) can trigger an inflammatory response leading to changes of circu-lating blood leukocyte (lymphocytes, monocytes, neutrophils) amounts [10,15]. Therefore, we compared clinical parameters between the groups, and found the higher pulse and weight in the lower EF group without MI (Table 1). Additionally, literature suggests that the worse patient condition is, the higher chronic inflammation patient have [24,25]. Therefore, we expected to find the higher number of monocytes and neutrophils in the patients with lower EF. However, we found only lymphocyte percentage lower in the lower EF group without MI. The interesting finding was the correlation between BMI and neutrophil count. Patients' weight correlated with neutrophil and monocyte count as well.

The activation of the hypothalamic-pituitary-adrenal axis leads to the stimulation of cortisol secretion and finally, to lymphopenia [26]. Therefore, our founded lymphocyte percentage decreasing in the lower EF group without MI seems logical and supports the knowledge, that the lower the EF is, the more stressful condition the patients have.

Excess of adipose tissue is shown to produce chemokines, leading to neutrophils [27] and monocytes [28] activation, which leads to macrophage recruitment [29] and differentiation into pro-inflammatory subset M1 [30], which releases additionally number of cytokines, producing a systemic pro-inflammatory condition. Despite the mechanisms

of heart response to systemic low-grade inflammation in overweight patients having not been explored fully yet, our findings—that BMI and patients weight correlated with neutrophil count—supplement the opinion that overweight takes place in low-inflammation maintenance in chronic HF without MI patients.

Interesting finding was, that LYM/MON was lower in the lower EF group without MI and monocyte count and percentage correlated with NT-proBNP and creatinine concentration. Additionally, LYM/MON reversibly correlated with NT-proBNP, uric acid, creatinine concentrations, and positively correlated with glomerular filtration rate (GFR). Our findings are in consensus with other research. N. Kose found lower LYM/MON in stable angina pectoris patients' group in comparison with normal coronary arteries and stated LYM/MON was an independent predictor of the high SYNTAX scores in patients with stabile angina pectoris [31]. The other research group found LYM/MON ≤ 2 to be an independent predictor of mortality with aHR of 1.67 (95% CI 1.03–2.69), $p = 0.035$, after adjusting for age, sex, ejection fraction, and NYHA class in chronic HF patients [32]. They found LYM/MON inversely correlated with NT-proBNP levels ($r = -0.463$, $p < 0.001$) and NYHA functional class ($r = -0.423$, $p < 0.001$). All these findings show the possibility of using LYM/MON as additional reading for evaluation of patients' functional condition.

Red blood cells (RBC) are heterogenous in size in adult humans and are measured as RDW. RDW can be expressed in absolute values as the standard deviation (SD) or as the coefficient of variation (RDW-CV) of erythrocyte volumes [20]. The normal RDW-CV is 11.5–14.6% [33]. An increase of RDW is called anisocytosis. Anisocytosis has been shown to have important consequences on adverse cardiovascular events [34] and mortality in HF patients [35]. Inflammation is shown to be related to anisocytosis too [36]. Our findings revealed higher RDW-CV than normal in chronic HF without MI patients with reduced EF. It should be noted that each 1% increase in RDW is associated with 10–19% higher risk (HR = 1.15; 95%l:1.05–1.26) of developing symptomatic HF and hospitalization [37–39]. Interestingly, we found RDW-CV conversely correlated with lymphocyte count and GFR and positively correlated with NT-proBNP and creatinine concentration. Therefore, according to our findings RDW-CV could be considered as additional marker of heart dysfunction in chronic HF without MI patients.

MCHC is a reading for evaluation of hemoglobin content in the erythrocytes. Low MCHC is called hypochromia. Hypochromia is found to associate with higher NT-pro BNP, lower GFR and modestly correlates with indices of left and right ventricular diastolic dysfunction. Additionally, MCHC levels were associated with higher risk of death or hospitalization of HFrEF patients [40]. Our findings are in consensus with Sinbaqueba C. et al.'s results [40]. We found the MCHC lower in the group with lower EF and that MCHC conversely corelated with NT-proBNP and positively correlated with GFR. These findings allow to take notice of the relative decrease of MCHC in the chronic HF without MI patients.

It is known that HFrEF most often develops because of cardiomyocytes death due to acute coronary syndrome [9]. Ischemic heart disease is usually caused by hyperlipidemia. The HFpEF can turn into HFrEF despite absence of MI. Therefore, we separated the HFrEF patients into groups according to presence of MI, so that we can compare differences in inflammatory, hematological, and lipidogram readings between these different chronic HF phenotypes. The most important finding was higher CRP and creatinine concentration and lower GFR in HFrEF with MI indicating the worse patients' condition and higher inflammatory environment. Other research has found higher CRP in lower EF in HFrEF patients not separated according to MI presence [11]. There are some studies where increased CRP was found both in HFrEF and HFpEF in compare with control group, but patients were not separated according to MI presence or other HF reasons there [41,42]. In our study, CRP does not differ between the groups with preserved and reduced EF without MI. Therefore, the discrepancy we think may be because of not the same grouping and smaller number of cases in our study. According to our findings it seems HFrEF with MI have more inflammatory condition than without MI. Atherosclerosis and acute myocardial

ischemia is associated with inflammation [43,44] because of apoptosis and necrosis [45]. Inflammation eventually becomes chronic and low-grade. Activation of the immune system leads to a rise in CRP [46] and low increase the monocyte count [47]. We do not find a statistically significant increase of monocyte or neutrophil counts in HFrEF with MI group, which is what we expected. Additionally, monocyte count and percentage correlated with creatinine concentration and NT-proBNP in our study. It was shown in the literature that blood monocyte count is increased in chronic kidney disease patients and independently associates with GFR [48,49], indicating the worse patient's condition. It is known GFR is estimated by using serum creatinine levels [50]. Another study showed that lower urinary creatinine (measured in morning spot urine) was associated with higher NYHA functional class in HF patients [51]. We think our findings are in consensus with the results presented in the literature. Again, low increase in monocyte count suggests a worse condition.

We think that an important finding is the lower HDL in HFrEF with the MI group and that HDL concentration inversely correlated with monocyte count and percentage. Low HDL levels were found to be associated with unfavorable prognosis in HF patients independent of the etiology and these levels may be a biomarker even for ongoing tissue inflammation [52]. Hepatic receptors SR-B1 bind HDL for cholesterol uptake. Lacking these receptors or its activity, leads to reduced capacity to carry out cholesterol efflux, a decreased antioxidative property promoting increased oxidative stress, and reduced anti-inflammatory signaling [53]. Therefore, HDL function appears to have an influence on myocardial remodeling. Inverse correlation between monocyte count and HDL confirms the interfaces between low grade inflammation and HDL concentration.

We found hematological readings—MCHC correlated with CRP, and LVEF correlated with MCHC and RDW-CV. A similar result was obtained in the HFrEF without MI. Again, both MCHC and RDW-CV may be relevant in assessing the overall condition of the HFrEF patient.

Summarizing, to the best of our knowledge, inflammation, hematological readings, and lipidogram were compared between HFrEF with and without MI in disease history and between the groups according to EF in patients without MI for the first time.

Our findings revealed higher pro-inflammatory condition and higher stress in the HFrEF group without MI in comparison with HFpEF without MI. Despite these findings, we can not give the specific limits, the results of our work give the presumption that LYM/MON can be appropriate as additional reading for evaluation of functional condition in chronic HF.

It seems inflammation environment could be higher in HFrEF with MI in disease history in comparison with those without MI. HDL concentration inversely correlated with monocyte count and percentage could show relation between the low-grade inflammation and lipid metabolism in HFrEF.

Both MCHC and RDW-CV may be relevant in assessing the chronic HF patients' condition.

5. Limitations

Our study has some limitations. The first one is not big number of cases. The second is that the study was performed according to patients' data received from medical history. Therefore, we cannot evaluate more precise inflammation readings like interleukins, tumor necrosis factor, or high sensitivity CRP, and lipoprotein metabolism readings like apolipoproteins concentration.

6. Conclusions

CRP concentration was higher and HDL cholesterol concentration was lower in the HFrEF group with MI in their medical history. Monocyte count and percentage reversible correlated with HDL cholesterol concentration and BMI correlated with neutrophil count.

Lymphocyte percentage, LYM/MON, and MCHC were lower, and RDW-CV was higher in the HFrEF group without MI.

Monocyte and lymphocyte count correlated with patients' condition reflected readings NT-proBNP, serum creatinine, uric acid concentrations; MCHC correlated with CRP, and LVEF correlated with MCHC and RDW-CV in all the groups.

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