

Cell and Organ Transplantation. 2022; 10(2): 74-79.
<https://doi.org/10.22494/cot.v10i2.141>

Subpopulations of lymphocytes and monocytes in blood of patients with atrial fibrillation or atrial flutter associated with hypertension



Talaieva T., Sychov O., Marchenko O.*, Tretyak I., Vasylynychuk N., Getman T., Romanova O., Stasyshena O., Vavilova L.

M. D. Strazhesko National Scientific Center of Cardiology, Clinical and Regenerative Medicine,
National Academy of Medical Sciences of Ukraine, Kyiv, Ukraine

*Corresponding author's e-mail: olena.ilchyshyna25@gmail.com

ABSTRACT

Atrial fibrillation (AF) remains one of the most common arrhythmias, second only to supraventricular extrasystoles, but the universal cause of its occurrence is still unknown. The inflammatory theory of arrhythmogenesis attracts the researcher's attention around the world.

THE PURPOSE of the study is to compare the subpopulations of lymphocytes and monocytes in blood of patients with paroxysmal and persistent forms of atrial fibrillation or atrial flutter (AFL) that are associated with arterial hypertension.

MATERIALS AND METHODS. The study involved 103 patients with atrial fibrillation and flutter that occurred secondary to hypertension. Depending on the form of arrhythmia, they were divided into three main groups: group I – with paroxysmal form of atrial fibrillation, group II – with a persistent form of atrial fibrillation, group III – with a persistent form of atrial flutter. The control groups included patients with hypertension, but without these arrhythmias and healthy individuals who entered groups IV and V, respectively. The lymphocytes and monocytes subpopulation was assessed by flow cytometry in peripheral blood.

RESULTS AND DISCUSSION. Analyzing the lymphocyte subpopulations in peripheral blood of patients with atrial fibrillation and flutter (groups I, II and III), it was found that the number of cells with cytotoxic activity (NK and NKT) in both absolute count and percentage values was significantly higher than in healthy individuals. A statistically significant decrease of T-regulatory cells number was found in patients with arrhythmias compared to control groups ($p \leq 0.05$). In patients with AF and AFL associated with hypertension, compared to patients with hypertension without these rhythm disturbances or healthy individuals, there is an increased number of classical and intermediate monocytes subpopulations.

CONCLUSIONS. In patients with atrial fibrillation and atrial flutter that occurred as a result of hypertension, compared to patients without arrhythmias or healthy people, there is an increased content of pro-inflammatory subpopulations of blood monocytes, T-cytotoxic cells and a decrease in the content of T-regulatory cells.

KEY WORDS: atrial fibrillation; atrial flutter; arterial hypertension; lymphocytes; monocytes

Cardiac arrhythmias are a common symptom of the most spread cardiovascular diseases, in particular nonvalvular atrial fibrillation (AF), occurs in 1.5 % of the total population. Epidemiological studies suggest that atrial flutter (AFL) is less common than AF – in about 0.09 % of the population, and isolated AFL – only in 0.037 % of cases. [1]. Flutter occurs more frequently in men and its detection increases significantly with age. The authors also associate AFL development with arterial hypertension, coronary heart disease, heart failure (HF) and is quite common in patients with chronic obstructive pulmonary disease, mitral or tricuspid heart valve involvement. [2]. A lot of Framingham study sub-analyses, which deservedly became a classic one, showed a clear link between AF and AFL

and the occurrence of transient ischemic attack, cardioembolic or hemorrhagic stroke, systemic thrombosis, HF progression, which leads to an increased number of hospitalizations, a deterioration of patients life quality, disability of working population [3]. But, despite a significant number of studies on the causes of AF and AFL, preventing complications, relapse or progression, the question of etiology and pathogenesis remains poorly understood.

Acute or chronic hemodynamic, metabolic disorders and the development of local inflammatory processes in the myocardium, which can lead to atrial arrhythmogenic remodeling, which contributes to the development and progression of AF, are considered as pathogenesis mechanisms

for the AF or AFL episode occurrence [5]. Fibrotic myocardial changes can become a substrate for the arrhythmogenic focus formation. Researchers consider fibrosis as an overgrowth of the connective tissue matrix as a result of local inflammation activation and oxidant stress arising from the inflammatory blood cells infiltration [6]. Oxidant stress is further enhanced by the renin-angiotensin system (RAS) activation, which stimulates the activation of NADH oxidase with subsequent production of IL-1, IL-6, Tumor Necrosis Factor alpha (TNF α) and Monocyte Chemoattractant Protein 1 (MCP-1), which trigger fibrous changes in the myocardium and associated electrical and structural remodeling typical for AF and AFL [7].

With the activation of local inflammation, as well as with chronic pressure overload, the synthesis of the main extracellular matrix components is activated: glycoproteins and proteoglycans, hyaluronic acid, which leads to fibrosis and myocardial hypertrophy. The main glycoprotein of the extracellular matrix is collagen produced by fibroblasts. An important point of the myocardial fibrosis development is fibroblasts transformation into myofibroblasts, characterized by 2 times greater ability to produce collagen. They are more sensitive to pro-inflammatory and profibrotic stimuli and are able to produce cytokines and chemokines themselves [8]. Normally, myofibroblasts are not presented in the myocardium, excluding heart valves. The formation of myofibroblasts occurs under the influence of pro-inflammatory cytokines and growth factors. Cells that are directly involved into the development and progression of systemic and local inflammation are blood monocytes. The monocytes modulate the inflammation by producing both pro- and anti-inflammatory cytokines, turning into macrophages with a pro- and anti-inflammatory phenotype. For the first time, the subpopulations of monocytes were isolated in 1988 by flow cytometry. They are divided into "classical" CD14^{hi}CD16⁻, and "non-classical" CD14^{hi}CD16⁺ and CD14^{dim}CD16⁺⁺. In 2010 they were classified as "classical", "intermediate" and "non-classical" or "patrolling", respectively [9]. Monocytes of classical subpopulation due to high expression of C-C chemokine receptor type 2 (CCR 2) to MCP-1 and L-selectin (CD62L) are able to migrate to the site of inflammation, where they perform effector functions, they are differentiated into inflammatory macrophages or into antigen-presenting dendritic cells [10]. Until today, the question of the functional role of various subpopulations of blood monocytes is being discussed. Thus, activated CD14^{hi}CD16⁻ monocytes have high phagocytic activity, secrete antimicrobial factors, active forms of oxygen, NO, myeloperoxidase, chemokines, stimulate the proliferation of T-effectors [11]. Intermediate CD14^{hi}CD16⁺ monocytes subpopulation is characterized by moderate phagocytic activity, limited ability to respiratory burst and chemokine synthesis while actively synthesizing pro-inflammatory cytokines (TNF α , IL-1 β , IL-6), which has recently been attributed to the monocytes of the classical subpopulation too. Due to these features, monocytes of classical and intermediate subpopulations are able to maintain an active inflammatory reaction and take part in tissue damage, including myocardial injury [12].

The high concentration of the fractalkine receptor CX3CR1 allows the monocyte subpopulation CD14^{dim}CD16⁺⁺ to transmigrate through the intact vascular endothelium, which led to the naming of this subpopulation as "patrolling", since these cells are able to attach to the vascular endothelium, move along capillaries, shallow veins and arteries, and monitor the state of the endothelium [13]. According to researchers, the monocytes subpopulation that have anti-inflammatory properties plays a leading role in the process of myocardial repair and remodeling prevention in acute myocardial infarction, contributing to the accumulation of myofibroblasts, angiogenesis and collagen production [14].

The **PURPOSE** of the study was to compare the subpopulation of lymphocytes and blood monocytes in patients with paroxysmal and persistent forms of atrial fibrillation or atrial flutter associated with arterial hypertension.

MATERIALS AND METHODS

The study included 103 patients with paroxysmal and persistent forms of atrial fibrillation and atrial flutter: 59 men (57.3 %) and 44 women (42.7 %) who were hospitalized in the Department of Clinical Arrhythmology and Electrophysiology of the M. D. Strazhesko National Scientific Center "Institute of Cardiology, Clinical and Regenerative Medicine NAMS of Ukraine". All patients were included into the study after signing an informed consent. The average age of patients was 55.4 \pm 4.6 years (from 21 to 69 years). In 11 (11.2 %) patients arrhythmia was registered for the first time, and, therefore, had a low-asymptomatic course. All patients had concomitant arterial hypertension. In 22 % of cases, cardiac rhythm disturbances occurred on the background of coronary heart disease, in 16 % – myocardial fibrosis (mainly in younger patients) and in 15 % – metabolic cardiomyopathy (prevailed among women). In other cases (47 %), the main diagnosis was hypertensive heart disease. Manifestations of heart failure occurred in the majority of subjects. Among patients with heart failure, 65 % of people had HF class I, HF class IIA – in 35 %. The New York Heart Association (NYHA) functional class of HF varied depending on the treatment regimen and how quickly the rhythm disturbance was eliminated. Younger patients, for the most part, did not have clinical and objective manifestations of HF, because of good compensatory capabilities of the body, even in the presence of arrhythmias, significant hemodynamic disorders did not occur.

The exclusion criteria were: unstable coronary artery disease, acute coronary syndrome with and without ST segment elevation, past acute Q-myocardial infarction, HF higher than NYHA functional class II or rapid progression of congestive HF, dilated and hypertrophic cardiomyopathy, acute or chronic myocarditis, presence of congenital and severe acquired heart defects, including rheumatic origin, decompensation of severe comorbidities, including diabetes mellitus, dysfunction of the thyroid gland, and stroke.

Patients with cardiac rhythm disturbances were divided into three main groups: I (n = 35) – with paroxysmal atrial fibrillation, II (n = 38) – with a persistent form of atrial fibrillation, III (n = 30) – with a persistent form of atrial flutter. For comparison, IV (n = 23) – with hypertension without arrhythmias, V (n = 21) – healthy individuals.

The examination and treatment of all patients was carried out in accordance with the guidelines and recommendations of the Ukrainian Association of Cardiology, the European Society of Cardiology, European Heart Rhythm Association (EHRA) and the American Heart College. Clinical and anamnestic examination, determination of laboratory parameters, ECG recording and analysis were carried out, ultrasound heart examination was performed – echocardiography (EchoCG), transesophageal echocardiography (TEE) in cases of sinus rhythm recovery and daily blood pressure monitoring (DBPM).

Angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor type 1 blockers (ARB), as drugs of "upstream therapy" of AF and, if necessary, their combinations with antihypertensive drugs were used to control blood pressure. The maximum possible correction of the manifestations of HF and concomitant diseases was carried out. In the presence of 2 or more points on the CHA₂DS₂ VASc score, the majority of patients received anticoagulant therapy. In order to prevent recurrence of arrhythmias, antiarrhythmic therapy was prescribed, mostly class IC drugs (propafenone and flecainide) and class III antiarrhythmic drug amiodarone. There were only two patients treated with amiodarone at the start of the study, which could not affect the ability of monocytes to produce cytokines and chemokines in general, especially on the subpopulations of these cells.

To determine the subpopulations of peripheral blood cells (lymphocytes and monocytes), flow cytometry with monoclonal antibodies (CD45/CD4/CD8/CD3 kit, CD45/CD56/CD19/CD3 kit, CD25, CD5, CD127, CD14, CD16) was performed. The following lymphocyte subpopulations were determined: CD3⁺CD19⁺ B-lymphocytes, CD3⁺ T-lymphocytes,

CD3⁺4⁺ T-helper cells (Th), CD3⁺8⁺ cytotoxic T-cells (T_{cyt}), CD3⁺56⁺ T-lymphocytes with natural killer activity (NKT), CD3⁺56⁺ natural killer cells (NK), CD4⁺25⁺127⁻regulatory T-cells (T_{reg}). Monocytes were also investigated, which, according to the level of expression of CD14 and CD16, were divided into three subpopulations: CD14⁺hiCD16⁻, CD14⁺hiCD16⁺ and CD14⁺dimCD16⁺. The absolute count of studied cells per 1 μL of blood was determined, as well as their percentage: for NK and NKT, their percentage of the total number of lymphocytes, for T_{reg} cells the percentage of Th cells, for monocytes – the percentage of each subpopulation of the total number of monocytes.

The peripheral blood was collected in K₃EDTA tubes and 100 μL was incubated for 15-20 minutes protected from light using FITC-conjugated monoclonal antibody (mAb) to CD45, RD-1-conjugated mAb to CD4, ECD-conjugated mAb to CD8 and PC-7-conjugated mAb to CD3, or with a kit of FITC-conjugated mAb to CD45, RD-1-conjugated mAb to CD56, ECD-conjugated mAb to CD19 and PC-7-conjugated mAb to CD3 (Beckman Coulter Inc., USA). After incubation, the red blood cells were lysed using an OptiLyse lysing solution (Beckman Coulter Inc., USA), then cell suspension was washed by centrifugation and resuspended in a phosphate buffered saline (PBS). To determine the number of T_{reg} cells, 100 μL of peripheral blood was incubated for 15-20 minutes protected from light with a mixture of PE-conjugated mAb to CD127, PC5-conjugated mAb to CD25 and APC-conjugated mAb to CD4. Preparations of blood

samples for the analysis of monocytes were carried out in a similar way: 100 μL of peripheral blood was incubated with FITC-conjugated mAb to CD14, PE-conjugated mAb to CD16 and APC-conjugated mAb to CD45 for 15-20 minutes, red blood cells were lysed for 10 minutes, washed in PBS and fluorosphere FlowCount (Beckman Coulter Inc., USA) were added to determine the number of cells per μL of blood. Negative control (blood sample without the addition of monoclonal antibodies) and isotypic control with IgG₁ and IgG₂b (Beckman Coulter Inc., USA) were used to adjust the protocol. The data analysis was performed on the NAVIOS flow cytometer using Navios EX Software, v. 2.2 (Beckman Coulter Inc., USA). At least 4·10⁴ cells per sample were recorded to analysis.

Statistical data processing was carried out using the MS Excel (Microsoft, USA), SPSS (IBM, USA) and Statistica (StatSoft Inc., USA) software. The obtained data was checked for compliance with the normal law distribution using the Kolmogorov-Smirnov test. With a normal distribution of data for quantitative indicators, the mean and standard error of mean (Mean ± SEM) were calculated. The differences between the samples, which are divided according to the normal law, were evaluated according to parametric Student's t-test. In case of abnormal data distribution, they were represented as a median (Me) and interquartile range (IQR). The probability of the difference in the values of indicators in groups was checked using the non-parametric Mann-Whitney U test. The differences were considered statistically significant at p < 0.05.

RESULTS AND DISCUSSION

Analyzing the content of blood lymphocyte subpopulations in patients with paroxysmal and persistent forms of AF or AFL (groups I, II and III), it was found that the number of cells with cytotoxic activity (NK and NKT) in both absolute and percentage values was significantly higher than in

healthy individuals (group V) by 36 % in group I, by 67 % in group II and by 90 % in group III (p < 0.01), however, there was no probable difference in these indicators compared to the group IV of patients with hypertension (Table 1, Fig. 1).

Table 1. Percentage and quantitative values of lymphocyte subpopulations in blood of studied patients, Me [IQR].

Indicator	I (n = 35)	II (n = 38)	III (n = 30)	IV (n = 23)	V (n = 21)
NK cells, % of the total lymphocytes	11.9 [9.5-15.8] [#]	12.1 [8.8-17.8] [#]	12.3 [8.7-19.7]	13.3 [9.9-15.5] [#]	9.6 [7.7-12.6]
NK cells, cells/μL	242.1 [170.1-284.2] [#]	209.5 [164-282.7]	211.5 [157-373.5]	241.5 [203.7-337.0] [#]	152.0 [132.5-220.0]
NKT cells, % of the total lymphocytes	5.2 [3.2-8.9]	6.3 [4.7-11.0] [#]	8.4 [3.5-10.9] [#]	7.5 [3.0-9.8] [#]	4.0 [2.6-5.6]
NKT cells, cells/μL	98.0 [58.1-155.0] [#]	120.5 [66.7-205.2] [#]	137.5 [63.7-186.7] [#]	118.0 [70.0-173.0] [#]	72.0 [37.5-89.5]
T _{reg} cells, % of T-helpers	6.8 [5.5-8.5] [*]	7.0 [4.7-8.1] [*]	7.1 [4.8-9.8]	8.5 [7.4-9.2] [#]	9.6 [9.1-10.0]
T _{reg} cells, cells/μL	54.0 [38.7-77.0] [*]	60.5 [34.2-73.7] [#]	63.0 [42.0-87.0] [#]	52.0 [39.7-75.7] [#]	97.0 [82.5-114.5]

Notes: * – p < 0.05 compared to group IV; # – p < 0.05 compared to group V.

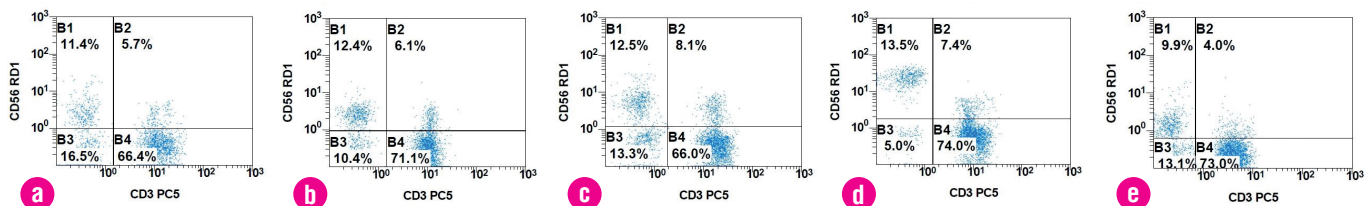


Fig. 1. Dot-plots of CD3 and CD56 expression on lymphocytes in peripheral blood of studied patients according to flow cytometry.

Notes: a – patients with paroxysmal AF; b – patients with a persistent AF; c – patients with a persistent form of AFL; d – patients with hypertension; e – healthy individuals. Quadrant B1 – natural killers (CD3⁺56⁺); quadrant B2 – NKT cells (CD3⁺56⁺); quadrant B4 – T-lymphocytes (CD3⁺).

The number of T-regulatory cells in patients with cardiac rhythm disturbances was significantly lower than in both healthy individuals and patients with hypertension. In absolute cell count, the number of T-regu-

latory cells was 44 % lower than normal in patients with paroxysmal AF (group I), by 38 % in patients with persistent AF (group II) and by 35 % in group III (patients with persistent AFL) (Fig. 2).

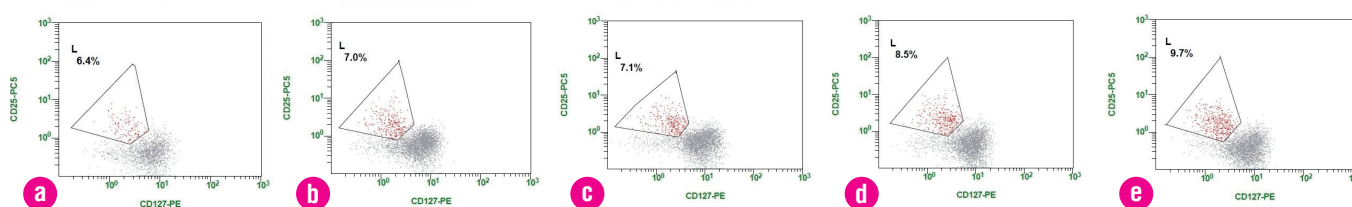


Fig. 2. Dot-plots of CD25 and CD127 expression on CD4⁺ lymphocytes in peripheral blood of studied patients according to flow cytometry.

Notes: a – patients with paroxysmal AF; b – patients with a persistent AF; c – patients with a persistent form of AFL; d – patients with hypertension; e – healthy individuals. Gate L – T_{reg} cells (CD127⁺25⁺).

According to the data presented in Table 2, it can be seen that the number of monocytes of the classical subpopulation was significantly higher in group II (persistent form of AF) and group III (persistent form of AFL) compared to group IV (patients with hypertension) and V (healthy

individuals). Intermediate monocyte subpopulations were found to be elevated in groups I (patients with paroxysmal AF) and II (persistent form of AFL) comparing quantitative data (Fig. 3).

Table 2. Percentage (of the total number of monocytes) and quantitative values of monocyte subpopulations in blood of studied patients, Me [IQR].

Group	I (n = 35)	II (n = 38)	III (n = 30)	IV (n = 23)	V (n = 21)
«Classical» monocytes, CD14 ⁺ 16 ⁻ , %	89.4 [81.8-89.9]	85.8 [83.0-86.6] [#]	91.1 [88.0-94.0] ^{***}	81.7 [78.0-87.5] ^{**}	86.7 [84.1-88.0] [*]
«Classical» CD14 ⁺ 16 ⁻ , cells/μL	298.0 [282.5-468.0]	409.5 [330.7-453.5] ^{***}	324.0 [238.0-417.0]	302.5 [282.7-364.8]	312.0 [254.0-405.0]
«Intermediate» monocytes CD14 ⁺ 16 ⁺ , %	8.0 [5.7-10.1]	8.1 [5.9-10.2]	7.0 [4.8-10.0]	8.0 [5.7-10.2]	7.2 [4.8-10.0]
«Intermediate» CD14 ⁺ 16 ⁺ , cells/μL	48.5 [33.7-73.2] ^{**}	52.5 [25.5-72.0] ^{**}	44.5 [24.7-62.5]	45.5 [38.7-58.2]	38.0 [28.5-45.5]
«Patrolling» monocytes CD14 ⁺ 16 ⁺ , %	6.4 [4.3-13.5] ^{***}	7.5 [6.0-10.8] ^{***}	5.47 [4.2-8.7] ^{***}	21.0 [15.5-25.5]	20.0 [13.0-28.5]
«Patrolling» CD14 ⁺ 16 ⁺ , cells/μL	20.0 [18.0-70.0]	39.5 [28.0-47.0] ^{**}	23.0 [19.3-38.0]	38.5 [26.0-46.8]	27.0 [19.5-34.0]

Notes: * – $p < 0.05$ compared to group IV; ** – $p < 0.05$ compared to group V; # – $p < 0.05$ compared to group III.

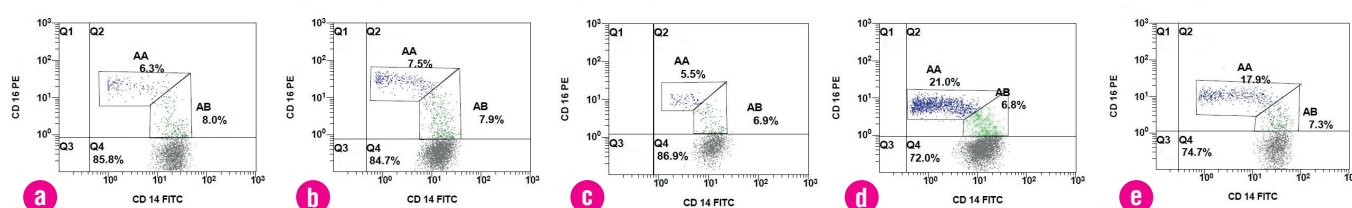


Fig. 3. Dot-plots of CD14 and CD16 expression on monocytes in peripheral blood of the studied patients according to flow cytometry.

Notes: a – patients with paroxysmal AF; b – patients with a persistent AF; c – patients with a persistent form of AFL; d – patients with hypertension; e – healthy individuals. Quadrant Q4 – «classical» monocytes (CD14⁺16⁻); gate AB – «intermediate» monocytes (CD14⁺16⁺); gate AA – «patrolling» monocytes (CD14⁺16⁺).

These fractions of monocytes can produce pro-inflammatory cytokines and growth factors, which leads to the activation of local inflammation, oxidant stress, local renin-angiotensin system, thus, triggering the processes of fibrosis in the myocardium. Patrolling monocytes were significantly less in percentage in all groups of patients with cardiac rhythm disturbances. The association between the severity of pathological myocardial remodeling and monocyte levels was also confirmed in the study of Suzuki A. et al. by a correlation analysis [15].

To date, the only reason for the development of atrial fibrillation and atrial flutter has not been established. There is clear evidence that in the process of formation of an arrhythmogenic focus, the activation of local RAS, local inflammation and oxidant stress plays a key role [16].

The obtained data on the composition of monocytes in the blood of patients with AF and AFL indicate an increase in the content of classical and intermediate subpopulations involved in the development of systemic and local inflammation, oxidant stress and activation of local and sys-

temic RAS, which, in turn, can lead to electrical and structural myocardial remodeling. The monocytes of these subpopulations produce pro-inflammatory cytokines such as IL-6, TNF- α and IL-1 β [17].

In addition, in patients with cardiac rhythm disturbances, the number of T-regulatory cells was significantly lower than in both healthy individuals and patients with hypertension. T_{reg} cells are a specialized subpopulation of T-cells that suppress the immune response, can inhibit the proliferation of T-cells, the production of cytokines, inhibiting the activity of systemic inflammation and the activation of autoimmune reactions [18]. Thus, a decrease in this cell number in patients with AF and AFL can lead to increasing the inflammation activity and blood monocytes. The authors note that in patients with type 2 diabetes, there are a decreased number of T_{reg} cells with an increased level of Th17, which contributes to the development of systemic inflammation [19].

In a study conducted by Shahid F. et al., it was shown that the content of the pro-inflammatory cytokine TNF- α , which is produced mainly by monocytes and macrophages, was likely elevated in patients with AF compared to individuals with sinus rhythm [20]. TNF- α levels correlated with leukocyte infiltration and more pronounced fibrous changes in the atria, which may have been the cause of AF. The role of inflammation in the AF and AFL development is also confirmed by a correlation with the C-reactive protein (CRP) level in patients with cardiac rhythm disturbances compared to those without them. It was found that in patients after ablation of additional pathways, the level of CRP is a surrogate marker of the risk of recurrence of tachyarrhythmias.

Similar results were obtained in a study conducted on 44 patients with AF [13]. In these patients, there was an increase the content of the intermediate monocytes subpopulation in the peripheral blood, which negatively correlated with the blood flow in the left atrium during the sinus rhythm.

In the clinical study of Tapp L. D. et al., a significant increase in the content of the intermediate subpopulation of monocytes (CD14^{hi}16⁺) was found in the first days after the development of acute myocardial infarction (AMI) with ST segment elevation. At the same time, it was shown that an increased number of CD14^{hi}16⁻ monocytes on day 7 after AMI is negatively associated with myocardial repair after AMI. Increase in the amount of this monocytes fraction has been associated with the development of left ventricular dysfunction after AMI [21].

Further evidence of the heart fibrosis role in the AF development comes from experimental and clinical studies that demonstrate that the prevention of atrial fibrosis using up-stream therapy can delay the development of AF [22].

Research carried out over the past decade in leading scientific laboratories and clinics in many countries demonstrates that endothelial dysfunction can play a key role in the pathogenesis of hypertension and cardiac arrhythmias. At present, it is known that the endothelium is of primary importance in preventing myocardial damage in ischemia/reperfusion, which is due to their ability to maintain vascular homeostasis [23]. Thus, the development of endothelial dysfunction can affect the function of cardiomyocytes and fibroblasts and lead to remodeling of heart and blood vessels, which creates background for the development of cardiac arrhythmias. The influence of various factors causes a complex of changes in the structure and endothelium function, which further leads to a limitation of the blood supply to the myocardium and to ischemic myocardial injury. Endothelial dysfunction is associated with damage and accelerated apoptosis of the endothelial cells and, quite often, these changes occur earlier than the morphological and clinical signs of the disease appear [24]. Factors that can lead to the endothelial dysfunction development include pro-inflammatory cytokines and reactive oxygen species produced by activated cells of classical and intermediate subpopulations of blood monocytes, as demonstrated in this study.

CONCLUSION

- In patients with atrial fibrillation or atrial flutter associated with hypertension, compared to patients with hypertension without these rhythm disturbances or healthy people, there is an increased number of classical and intermediate monocytes fraction and a decreased content of T-regulatory cells in peripheral blood.***
- Patients with AF and AFL showed an increased number of cells with cytotoxic activity (NK and NKT) compared to healthy individuals, but there was no likely difference in these indicators compared to the group of patients with arterial hypertension without cardiac rhythm disturbances.***
- These changes can be one of the factors for the activation of systemic and local inflammatory processes that can lead to fibrosis in the myocardium and the associated electrical and structural remodeling typical for AF and AFL.***

REFERENCES:

1. *Kornej J, Börschel CS, Benjamin EJ, Schnabel RB.* Epidemiology of Atrial Fibrillation in the 21st Century. *Circulation Research.* 2020; 127:4-20. Available from: <https://doi.org/10.1161/circresaha.120.316340>
2. *Gerald V, Naccarelli, Helen Varker, Jay Lin, Kathy L.Schulman.* Increasing prevalence of Atrial Fibrillation and Flutter in the United States. *Am J Cardiol.* 2009; 104(11):1534-1539. Available from: <https://doi.org/https://doi.org/10.1016/j.amjcard.2009.07.022>
3. *Staerk L, Wang B, Preis SR, Larson MG, Lubitz SA, Ellinor PT, et al.* Lifetime risk of atrial fibrillation according to optimal, borderline, or elevated levels of risk factors: cohort study based on longitudinal data from the Framingham Heart Study. *BMJ.* 2018; 361:k1453. Available from: <https://doi.org/10.1136/bmj.k1453>
4. *Tsukamoto M, Seta N, Yoshimoto K.* CD14 bright CD16+ intermediate monocytes are induced by interleukin-10 and positively correlate with disease activity in rheumatoid arthritis. *Arthritis Res Ther.* 2017; 19(1):28. Available from: <https://doi.org/10.1186/s13075-016-1216-6>
5. *Verdecchia P, Angeli F, Reboldi G.* Hypertension and Atrial Fibrillation Doubts and Certainties From Basic and Clinical Studies. *Circulation Research.* 2018; 122(2):352-368. Available from: <https://doi.org/10.1161/circresaha.117.311402>
6. *Kallistratos M, Poulimenos LE, Manolis AJ.* Atrial fibrillation and arterial hypertension. *Pharmacol Res.* 2018; 128:322-326. Available from: <https://doi.org/10.1016/j.phrs.2017.10.007>
7. *Boos CJ, Anderson RA, Lip GYH.* Is atrial fibrillation an inflammatory disorder? *Eur Heart J.* 2006; 27(2):136-149. Available from: <https://doi.org/10.1093/eurheartj/ehi645>
8. *HuY-F, Chen YJ, Lin YJ, Chen SA.* Inflammation and the pathogenesis of atrial fibrillation. *Nat Rev Cardiol.* 2015; 12(4), 230-243. Available from: <https://doi.org/10.1038/nrcardio.2015.2>
9. *Ziegler-Heitbrock L, Hofer TP.* Toward a refined definition of monocyte subsets. *Front Immunol.* 2013; (4):23. Available from: <https://doi.org/10.3389/fimmu.2013.00023>
10. *Prabhu SD.* It takes two to tango: monocyte and macrophage duality in the infarcted heart. *Circ Res.* 2014; 114:1558-1560. Available from: <https://doi.org/10.1161/CIRCRESAHA.114.303933>
11. *Sprangers S, Vries T, Everts V.* Monocyte Heterogeneity: Consequences for Monocyte-Derived Immune Cells. *J Immunol Res.* 2016. Available from: <https://doi.org/10.1155/2016/1475435>
12. *Nahrendorf M, Pittet MJ, Swirski FK.* Monocytes: protagonists of infarct inflammation and repair after myocardial infarction. *Circulation.* 2010; 121:2437-2445. Available from: <https://doi.org/10.1161/CIRCULATIONAHA.109.916346>
13. *Suzuki A, Fukuzawa K, Yamashita T, Yoshida A, Sasaki N, Emoto T, et al.* Circulating intermediate CD14++CD16+ monocytes are increased in patients with atrial fibrillation and reflect the functional remodeling of the left atrium. *EP Europace.* 2017. 19(1):40-47. <https://doi.org/10.1093/europace/euv422>
14. *Ghatts A, Griffiths H R, Devitt A, Lip GYH, Shantsila E.* Monocytes in Coronary Artery Disease and Atherosclerosis: Where Are We Now? *J Am Coll Cardiol.* 2013; 62:1541-1551. Available from: <https://doi.org/10.1016/j.jacc.2013.07.043>
15. *Zharinov OY, Levchuk NP, Ikorkin MR, Sychev OS.* Prediction of prolonged sinus rhythm retention after cardioversion in patients with non-valvular persistent atrial fibrillation. *Lviv Clinical Bulletin.* 2014; 4(8): 2014.
16. *Joffe HV, Adler GK.* Effect of aldosterone and mineralocorticoid receptor blockade on vascular inflammation. *Heart Fail Rev.* 2005; 10:31-7. Available from: <https://doi.org/10.1007/s10741-005-2346-0>
17. *Zhang J, Yang L, Ding Y.* Effects of irbesartan on phenotypic alterations in monocytes and the inflammatory status of hypertensive patients with left ventricular hypertrophy. *BMC Cardiovascular Disorders.* 2021; 21:194. Available from: <https://doi.org/10.1186/s12872-021-02004-78>
18. *Kumar P, Saini S, Khan S, Surendra Lele S, Prabhakar BS.* Restoring self-tolerance in autoimmune diseases by enhancing regulatory T-cells. *Cell Immunol.* 2019; 339:41-49. Available from: <https://doi.org/10.1016/j.cellimm.2018.09.008>
19. *Bigdelou B, Reza S M, Najafikhoshnoo S, et al.* COVID-19 and Preexisting Comorbidities: Risks, Synergies, and Clinical Outcomes. *Front Immunol.* 2022; 13:890517. Available from: <https://doi.org/10.3389/fimmu.2022.890517>
20. *Shahid F, Lip GYH, Shantsila E.* Role of Monocytes in Heart Failure and Atrial Fibrillation. *JAHA.* 2018; 7(3):e007849. Available from: <https://doi.org/10.1161/jaha.117.007849>
21. *Tapp LD, Shantsila E, Wrigley BJ, Pamukcu B, Lip GYH.* The CD14++CD16+ monocyte subset and monocyte-platelet interactions in patients with ST-elevation myocardial infarction. *JTH.* 2012; 10(7). Available from: <https://doi.org/10.1111/j.1538-7836.2011.04603.x>
22. *Hindricks G, Potpara T, Dagres N, Arbelo E, Bax J, Blomström-Lundqvist C, et al.* ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. 2020. *Eur Heart J.* 2021; 42(5):373-498. Available from: <https://doi.org/10.1093/eurheartj/ehaa612>
23. *Herrera-Zelada N, Zuñiga-Cuevas U, Ramirez-Reyes A, Lavandero JA, Riquelme S.* Targeting the Endothelium to Achieve Cardioprotection. *Front Pharmacol.* 2021; 12:1-17. Available from: <https://doi.org/10.3389/fphar.2021.636134>
24. *Theofilis P, Sagris M, Oikonomou E, Antonopoulos AS, Siasos G, Tsioufis C, et al.* Inflammatory Mechanisms Contributing to Endothelial Dysfunction. *Biomedicines.* 2021; Available from: <https://doi.org/10.3390/biomedicines9070781>



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The authors declare that there is no potential conflict of interest regarding the research, authorship and/or publication of this article

УДК: 616.12-008.313+612.017+612.172

Особливості субпопуляційного складу лімфоцитів та моноцитів крові у пацієнтів з фібриляцією або тріпотінням передсердь на тлі артеріальної гіпертензії



Талаєва Т. В., Сичов О. С., Марченко О. Я., Третяк І. В., Василичук Н. М., Гетьман Т. В., Романова О. М., Стасишена О. В., Вавілова Л. Л.

ДУ «Національний науковий центр «Інститут кардіології, клінічної та регенеративної медицини імені акад. М. Д. Стражеска» НАМН України», Київ, Україна

РЕЗЮМЕ

Фібриляція передсердь залишається однією з найбільш поширених аритмій, поступаючись лише суправентрикулярній екстрасистолії, але універсальна причина її виникнення досі залишається невідомою. Запальна теорія аритмогенезу привертає до себе увагу дослідників з усього світу.

МЕТА РОБОТИ – порівняти показники субпопуляційного складу лімфоцитів та моноцитів крові у пацієнтів з пароксизмальною та персистою формами фібриляції або тріпотіння передсердь, що виникли на фоні артеріальної гіпертензії.

МАТЕРІАЛИ І МЕТОДИ. У дослідження було включено 103 пацієнти з фібриляцією або тріпотінням передсердь, що виникли на фоні артеріальної гіпертензії. Залежно від форми аритмії їх було розподілено на три основні групи: I група – з пароксизмальною формою фібриляції передсердь, II група – з персистою формою фібриляції передсердь, III група – з персистою формою тріпотіння передсердь. Як контроль порівняння були пацієнти з артеріальною гіпертензією, але без вищевказаних порушень ритму серця, та практично здорові особи. Пацієнтам проводилось визначення рівня в периферичній крові субпопуляційного складу лімфоцитів та моноцитів методом проточної цитометрії.

РЕЗУЛЬТАТИ ТА ОБГОВОРЕННЯ. При аналізі вмісту субпопуляцій лімфоцитів крові у пацієнтів з фібриляцією та тріпотінням передсердь (I, II та III групи) було виявлено, що кількість клітин з цитотоксичною активністю (натуральні кілери та Т-лімфоцити з кілерною активністю) як в абсолютних, так і у відсоткових значеннях була достовірно більшою, ніж у практично здорових осіб. Були виявлені статистично значимі менші показники кількості Т-регуляторних клітин у хворих з аритміями в порівнянні з контрольними пацієнтами ($p \leq 0,05$). У пацієнтів з фібриляцією передсердь та тріпотінням передсердь на тлі артеріальної гіпертензії в порівнянні з хворими з гіпертонічною хворобою без цих порушень ритму або здоровими особами встановлено більші значення кількості моноцитів класичної та проміжної субпопуляцій.

ВИСНОВКИ. У пацієнтів з фібриляцією та тріпотінням передсердь, що виникли на тлі артеріальної гіпертензії, у порівнянні з пацієнтами без аритмій чи здоровими людьми має місце підвищений вміст прозапальних субпопуляцій моноцитів крові, Т-цитотоксичних клітин та зниження вмісту Т-регуляторних клітин.

КЛЮЧОВІ СЛОВА: фібриляція передсердь; тріпотіння передсердь; артеріальна гіпертензія; лімфоцити; моноцити