МЕДИЦИНСКИЕ НАУКИ

THE ROLE OF INFLAMMATION AND COAGULATION CASCADE IN THE PATHOGENESIS OF ATRIAL FIBRILLATION.

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Abstract. Introduction: Atrial fibrillation (AF) is associated with prothrombotic or hypercoagulable states, various inflammation markers such as interleukin-6 (IL-6) and hsC-reactive protein (hsCRP) have also been associated with AF. The aim of this study is to investigate the relationship between inflammation markers and the prothrombotic state in the setting of AF and the impact on outcome in patients with AF.

Methods: We observed 141 patients with non-valvular AF. As a control group patients similar in gender and age without AF were examined. Clinical, instrumental and laboratory tests were performed on the observed patients. The markers of the coagulation cascade (TF and F) and of inflammatory markers (hsCRP and IL-6) were studied additionally by ELISA on the analyzer "Stat Fax 303 Plus". Studies were conducted using SPSS 13.0 and EXCEL-2013.

Results: The obtained results showed that compared to the control group, AF patients had significantly higher levels of IL-6 ($p = 0.043$), hsCRP ($p = 0.002$), TF ($p = 0.026$), and F ($p = 0.025$). Moreover, levels of hsCRP were higher among AF patients at "high" risk of stroke by CHA2DS2-VASc Score ($p = 0.003$). Besides, the levels of hsCRP and IL-6 were markedly elevated in patients with dilated left atrium ($p = 0.001$), poorly functioning left atrial appendage ($p = 0.023$) and longer duration of AF ($p = 0.002$).

Conclusion: We have demonstrated that the increased plasma levels of IL-6 and hsCRP are related to indices of the coagulation cascade and contribute to structural atrial remodeling in patients with AF.

Keywords: Atrial fibrillation; high sensitive C reactive protein; Interleukine-6; tissue factor; fibrinogen

Introduction: Atrial fibrillation (AF) is the most commonly sustained arrhythmia and at the same time the most heterogeneous arrhythmia with regard to the individual spectrum of resulting symptoms. AF is associated with atrial structural changes that may have an inflammatory basis [1, 2, 3, 4, 5, and 6]. The role of inflammation in the pathogenesis of AF has not yet been evaluated but inflammatory mechanisms may form a basis for new agents more likely to prevent recurrent episodes of AF. There has recently been much interest in the relationship between systemic inflammation and coagulation cascade in patients with AF [7, 8, and 9]. AF is also associated with a prothrombotic or hypercoagulable state and there is a plausible evidence linking inflammation to the initiation and perpetuation of AF and AF-related thrombosis. Several prothrombotic factors have been found to be elevated in AF, indicating abnormal thrombogenesis. Over the last years we suggested the link between inflammatory processes and development of AF. Classical markers of inflammation such as hsC-reactive protein (hsCRP) and proinflammation cytokine Interleukin –6 (IL-6) were found elevated in patients with AF. Tissue Factor (TF) is the principal initiator of the coagulation cascade. In this way TF promotes blood coagulation and is involved in inflammation and angiogenesis [10, 11, 12, and 13]. The aim of this study is to investigate the relationship between inflammation markers and the prothrombotic state in the setting of AF, including the impact of this interaction on clinical presentation and outcome in patients with AF.

Material and methods. We observed 141 patients with non-valvular AF. There were 84 males (59.2%), 57 females (40.8. %), mean age $59, 73 \pm 6, 49$, the duration of AF is $14, 36 \pm 12, 7$ months. Among the examined patients, 129 (92.4%) were diagnosed of ischemic heart disease, arterial hypertension was observed in 78 patients (56.1%). Heart failure (NYHA functional class I-II) was detected in 104 patients (76.4%) and NYHA (functional class III) - in 33 patients (23.6%). The exclusion criteria were: ventricular arrhythmia (more than 30 per hour by Lown) ventricular tachycardia, acute coronary syndrome, heart failure (functional class more than III by NYHA), bronchial asthma, diabetes, and acute inflammatory disease within the last 4 months, cardiomyopathy, myocarditis, valvular heart disease, the thyroid gland dysfunction. Clinical examination of patients included a study of medical history, physical, laboratory and instrumental examination. As a control group similar in gender and age composition 48 patients with IHD and AH without AF were examined. Clinical and instrumental characteristics of patients with AF were performed in Table 1.

The program of investigation included general clinical examination of patients: electrocardiogram, echocardiography and common biochemical blood tests. The level of the prothrombotic state, including markers of the coagulation cascade (TF and F) and levels of inflammatory markers (hsCRP and IL-6) were studied additionally and were determined by ELISA on the analyzer "Stat Fax 303 Plus». Studies were conducted on the basis of simple randomized protocols, using the universal statistical packages SPSS 13.0 and

EXCEL-2013. **Results:** The analysis of the data showed the significant differences between the levels of hsCRP and IL-6 among patients with AF and the control group (1.2 ± 0.60 vs. 5.7 ± 1.4 $p = 0.002$ and 1.2 ± 0.8 vs. 2.6 ± 1.1 $p = 0.043$ accordingly). HsCRP is an acute-phase protein that is why it is likely to react more quickly to the appearance of AF. In all likelihood the inflammation markers such as hsCRP and IL-6 markers of inflammation can be considered as risk factors for the occurrence and recurrence of AF. At the same time, the state of coagulation cascade of blood is of particular importance for the appearance of AF. Tissue Factor (TF), formerly known as thromboplastin, is the key initiator of the coagulation cascade. TF expression and activity can be induced in endothelial cells, vascular smooth muscle cells, and monocytes by various stimuli such as cytokines, growth factors, and biogenic amines. We revealed that in patients with AF, TF is improved as compared to the similar patients without AF (1300 ± 50 vs 600 ± 11.9 $p = 0.026$). The similar pattern was also observed when comparing the concentrations of fibrinogen F in AF patients with control group ($13. \pm 2.4$ vs 9.08 ± 1.4 $p = 0.025$). Moreover, we found a direct correlation between the activity of thromboplastin and the left atrium structural and functional changes ($r = 0.643$). Table 2 shows the results of concentration of some inflammatory markers and coagulation cascade agents in patients with AF and the similar patients without AF as a control group (table 2).

Thus, our obtained results showed that compared to the control group, AF patients had significantly higher levels of IL-6 ($p = 0.043$), hsCRP ($p = 0.002$), TF ($p = 0.026$), and F ($p = 0.025$). Moreover, plasma levels of hsCRP were higher among AF patients at "high" risk of stroke by CHA2DS2-VASc Score ($p = 0.003$). Besides the levels of hsCRP and IL-6 are markedly elevated in patients with dilated left atrium ($p = 0.001$), poorly functioning left atrial appendage ($p = 0.023$) and longer duration of AF ($p = 0.002$).

Conclusion: Thus, as a classic inflammatory marker hsCRP is the major acute phase protein and a sensitive indicator of inflammation. HsCRP elevation may be a non-specific response to any environmental stimulus, also it may be not directly or indirectly related to the pathogenesis of AF. Its synthesis by the liver is regulated to a large extent by the pro-inflammatory cytokine (such as IL-6), and probably acting on distance to the blood vessel wall to produce elevations in conventional cardiovascular risk factors and the coagulation cascade agents such as TF and F. That is why we have demonstrated that the increased plasma levels of IL-6 and hsCRP are related to indices of the coagulation cascade and may contribute to structural atrial remodeling in patients with AF.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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Tables

Table 1.

Characteristics of the average values of some parameters of patients with AF

Indices	Mean values+standards deviation
Age (years)	59,7 ± 6,49
Duration AF (months)	14,4 ± 12,7
LAD (mm)	42,28 ± 3,68
LVEDD (mm)	56, 69 ± 3, 84
EF (%)	46, 63 ± 5, 48
IVST (mm)	12.44 ± 2, 50

Note: LAD-left atrium diameters; LVEDD-left ventricular end-diastolic diameter; EF – ejection fraction; IVST - interventricular septum thickness;

Table 2.

The levels of inflammation markers and coagulation cascade agents in AF patients and the control group

Indices	Control group n=48	AF group n=141
TF pg/ml	600±11.9	1300± 50.* p = 0.026
IL-6 pg/ml	1.2± 0.8	2.6± 1.1* p = 0.043
hsCRP mg/l	1.2±0.60	5,7± 1.4* p = 0.002
F mgmol/l	9.08± 1.4	13. ± 2.4* p = 0.025

Notes: TF – tissue factor; F – fibrinogen; hsCRP – hsC reactive protein; IL-6 – cytokine interleukin -6.

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**QUANTUM BIOPHYSICS IN CONVALESCENCE OF NOSOLOGICAL FORMS
(ON THE EXAMPLE OF MULTIPLE SCLEROSIS).
PREPARATION AND STORAGE OF ENTANGLED STATES IN NONLINEAR CRYSTALS**

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