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Plasma markers of myocardial inflammation at isolated atrial fibrillation

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Abstract

Background: Atrial fibrillation (AF) is one of the widest spread forms of arrhythmia, which is associated with the increased mortality and thromboembolic complications. To date, the involvement of renin-angiotensin-aldosterone system and immunomediators of inflammation into the mechanisms of development and maintenance of isolated AF is not clear. Specificity of their changes with respect to the latent myocarditis at AF is not proved.

Methods: In 96 patients with persistent isolated atrial fibrillation (IsAF), scheduled for radiofrequency ablation and endomyocardial biopsy (EMB), and in 20 healthy volunteers (HVT), levels of plasma tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, IL-6, IL-8, IL-10, fatty acid-binding protein (FABP), neopterin, C-reactive protein (CRP) were determined by ELISA, level of aldosterone and the renin activity were determined by radioimmunoassay. Results were compared between the study and HVT groups and related to the EMB data.

Results: Endomyocardial biopsy revealed lymphocytic myocarditis in 29%, immunohistochemical signs of viruses' persistence in the myocardium—in 43.8% of patient. We formed 4 subgroups: «myocarditis», «fibrosis», «virus positive», «virus negative». In the group «myocarditis», level of IL-6 was significantly higher than in group «fibrosis» ($P < .01$). ROC analysis showed its sensitivity 75%, specificity 75% (AUC = 0.759, Cutoff Value > 1.6 pg/mL, $P < .01$). In the group «virus positive», level of neopterin was significantly higher than in group «virus negative» ($P < .01$), with sensitivity 51%, specificity 84% (AUC = 0.675, Cutoff Value > 13.2 nmol/L, $P < .01$).

Conclusion: Levels of plasma IL-6 and neopterin may serve as a marker of latent viral myocarditis in IsAF.

KEYWORDS
atrial fibrillation, cytokine, inflammation, myocarditis, neopterin

1 | INTRODUCTION

Atrial fibrillation (AF) is one of the most wide spread forms of arrhythmia. Its morbidity in general population is 1%-2%, and among of all forms of rhythm disorders, its value is equal to 35%-45%.[1,2] It is commonly known that AF is associated with the increased death risk, cerebral stroke, and other thromboembolic disorders.[1–4]

According to Saxena et al, the main causes of AF are arterial hypertension (40%), coronary artery disease (CAD) (16.6%) and myocardium diseases (15.4%).[2] Also in 10-30% of patients, it is impossible to find the cause of the arrhythmia. It has been proposed that chronic latent myocarditis, including those of virus nature, may be one of the factors of initiating and maintenance of AF.[5–8] Myocardial inflammation can also lead to atrial remodeling and reduce the effectiveness of interventional treatment of the arrhythmia.

It is known, that renin-angiotensin-aldosterone system (RAS) is a significant part of the neuroendocrine regulation of the human cardiovascular system.

To date, it was shown that RAS activation plays an important role in the pathogenesis of AF, promoting an increasing of proinflammatory cytokines (interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor alpha (TNF-α), interferon-gamma (INF-γ)), chemoattractant proteins, and selectins blood and tissue levels, which leads to maintenance of inflammation in the atria.[4,5]

The cascade of reactions, initiated by immunomediators of inflammation, has a damaging effect on cardiomyocytes, interstitial structures, and the conduction system of the myocardium.[6] Proinflammatory cytokines also stimulate the deposition of collagen in the cardiac muscle, resulting in fibrosis, hypertrophy of cardiomyocytes, and arrhythmogenic substrate formation.[7]

To date, the involvement of RAS and immunomediators of inflammation in the mechanisms of development and maintenance of AF, complicated by coronary artery disease (CAD) or arterial hypertension (AH), is established.[8,9] At the same time, the role of these blood markers in the pathogenesis of isolated AF (IsAF) is not clear. The question concerning specificity of their changes with respect to the latent myocarditis also remains open.

1.1 | Aim

To analyze the relationship between plasma renin, aldosterone, inflammatory markers and presence of latent myocarditis in patients with isolated atrial fibrillation.

2 | METHODS

Plasma samples from 96 patients (75 men, 21 women, mean age 46.8 $\pm$ 10.7 years) with persistent isolated (unclear etiology) atrial fibrillation, scheduled for radiofrequency ablation and endomyocardial biopsy (EMB) in the department of surgical treatment of complex cardiac rhythm abnormalities and pacing of the Cardiology Research Institute, Tomsk National Research Medical Center, Russian Academy of Science, were analyzed. All patients underwent clinical examination, ECG, echocardiography, and blood samples were taken from the forearm vein. IsAF was defined and managed, according to current guidelines.[1]

We applied the following inclusion criteria:

The age of patients 18-60 years without regard to gender; persistent form of IsAF; refractoriness to antiarrhythmic therapy; left atrial volume—less than 150 mL (according to intravenous contrast computed tomography); absence of intraventricular thrombus according to the data of transesophageal ultrasound scanning; absence of coronary artery stenosis according to the data from MSCT—coronary angiography. Informed consent was obtained from all individual participants included in the study. Baseline characteristics of these patients are shown in Table 1. All patients had persistent form of atrial fibrillation with median duration of the disease 5.7 $\pm$ 4.9 years. The heart failure (HF) according to NYHA was of 0-II class. Only 5.2% of examined subjects had no cardiac complains. Parameters of the left ventricular (LV) contractility function according to the echocardiography were normal in most cases. Only 14.6% of subjects had local hypokinesia in LV. Also the most patients had no clinical or laboratory signs of acute inflammation, but in 4.2% of cases the moderate leukocytosis was found, in 22.9% the erythrocyte sedimentation rate higher than 15 mm/h and in 4.2% of cases subfibrillitis were observed.

We applied the following exclusion criteria:

Old myocardial infarction/acute myocardial infarction; patients with coronary artery disease (CAD), vulvular diseases; hypertension, thyrotoxicosis, diabetes, previous cardiac surgical operations, previous therapy with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), obesity, sleep apnea syndrome, alcohol consumption (more than 20 mL of an ethanol in a week).

In addition, plasma samples of 20 healthy volunteers (HVT) with sinus rhythm (12 women and 8 men, age 30 $\pm$ 5.1 years) were analyzed.

Exclusion criteria for HVT are as follows: presence of any myocardial, vulvular diseases, any kind of arrhythmia or conduction abnormality, hypertension, thyrotoxicosis, diabetes, previous cardiac surgical operations, acute or chronic infectious diseases.

Patients and HVT were included in the study after they signed informed consent.

The study was performed according to the standards of Good Clinical Practice and principles of the Declaration of Helsinki. The protocol of the study was approved by the ethical committee of the authors' institution (protocol №103, 28.03.2013). Informed consent was obtained from all individual participants included in the study

2.1 | Plasma sampling and analysis

Blood sampling was performed in the morning, after 10 hours fasting, into BD Vacutainer tubes with K2E EDTA and BD Vacutainer sprayed with silica on a 10 mL tube wall in each. The blood samples were centrifuged for 10 minutes at 1500 *g*. The resulting plasma

TABLE 1 Baseline characteristics of the patients with IsAF (n = 96)

Clinical characteristics	Value
Age, y	46.8 ± 10.7
Sex	
Female	21
Male	75
Weight (kg)	
Female	63 ± 7.2
Male	78 ± 10.4
BMI (kg/m^2)	
Female	21.83 ± 1.26
Male	23.08 ± 1.8
History of illness, y	5.7 ± 4.9
Cardialgia, n	17 (17.7%)
Dyspnea at moderate physical activity, n	34 (35.4%)
Transient palpitation, n	45 (46.9%)
Irregular heartbeat, n	31 (32.3%)
Continuous palpitation, n	15 (15.6%)
An episodic hypertension (no more than 140/90 mmHg), n	48 (50%)
Sleep apnea syndrome (yes)	0
Weakness, n	23 (23.9%)
Subfebrility, n	4 (4.2%)
Absence of complaints, n	5 (5.2%)
Infection causality, n	14 (14.6%)
Moderate leukocytosis, n	4 (4.2%)
Erythrocyte sedimentation rate higher than 15 mm/h, n	22 (22.9%)
Heart failure (HF) according to NYHA, n	
No	41 (42.7%)
HF I	39 (40.6%)
HF II	17 (17.7%)
Ejection fraction, (% M ± SD)	61.7 ± 12
End-diastolic volume of LV (mL), M ± SD	116.34 ± 28
End-systolic volume of LV (mL), M ± SD	45.5 ± 26.2
Left atrial volume, (sm^3), M ± m	109 ± 26
Local hypokinesia in LV, n	14 (14.6%)

were collected in small-sized tubes with the appropriate labeling and frozen at t −70°C. Samples of blood that underwent hemolysis were excluded from the study.

The plasma levels of proinflammatory cytokines: TNF-α, interleukin-1β (IL-1β), IL-8, IL-6, anti-inflammatory interleukin-10 (IL-10), and high-sensitivity C-reactive protein (hsCRP) were determined by enzyme-linked immunosorbent assay (ELISA) with test systems of the company «Vector-Best» (Russia). Plasma levels of the protein binding fatty acid (PBFA) and neopterin were determined using the Hycult Biotech and IBL test systems. All assays were performed using an Infinite F50 microplate counter and the Magellan Tracker software ("Tecan Austria GmbH", Austria).

In 70 patients, plasma renin activity (PRA) and aldosterone levels were determined by radioimmunoassay using «Beckman Coulter» kits (Czech Republic). We used norms defined in the instructions to the manufacturer's kit: aldosterone 30-355 pg/mL, for PRA 0.7-3.5 ng/mL/h.

2.2 | Endomyocardial biopsy

Samples for histological analysis were taken during ablation of AF. Right heart catherization was performed by transvenous access according to Seldinger technique under fluoroscopic guidance. Biopsy samples were taken segment by segment from the right ventricle (RV) apex, right ventricular outflow track, and interventricular septum using biotom Biopsy Forceps 7F, 50/100 sm (Cordis, USA).

Histological samples were placed in formalin, and tissues were unwatered by passing through spirit solutions with increasing concentration, further they were colored by hematoxylin-eosin, toluidine blue, according to Van Geison technique. Myocarditis was diagnosed in accordance with Dallas criteria.[10] The extent of fibrosis was quantified in accordance with the scale of fibrosis severity suggested by Calabrese et al.[11]

Biopsy samples were analyzed by immunohistochemistry for the presence of cardiotropic virus antigens and CD—immune cell antigen (mouse monoclonal antibody for immunohistochemistry to cytomegalovirus, parvovirus B19 virus type 6 virus, adenovirus, coxacky, enterovirus, CD45$^+$, CD4$^+$, CD8$^+$, Dako Cytomation, Denmark).

2.3 | Statistical analysis

Statistical analyses were performed using SPSS 20 software. A hypothesis for Gaussian distribution by Kolmogorov-Smirnov criterion was rejected. Variables were characterized by median (Me, lower-upper quartile). We checked the significant differences between groups with the Mann-Whitney test for nonnormal distribution.

Diagnostic efficiency of some markers (sensitivity, specificity) was analyzed using the ROC-curve method.

3 | RESULTS

3.1 | Plasma markers in patients with IsAF

Levels of analyzed markers are shown in the Table 2, where it can be seen, that concentration of all plasma inflammatory markers and neopterin in patients with IsAF were significantly higher than in the HVT group.

At the same time, levels of anti-inflammatory cytokine IL-10 and PBFA were not significantly differ from the HVT and the parameters of RAS, in particular, the concentration of aldosterone and PRA in all patients of the study group was within the norm range and therefore were not used for further analysis.

TABLE 2 Plasma levels of inflammatory and RAS markers in patients with IsAF compared with HVT

Marker	Patient with IsAF n = 96 (Me, lower-upper quartile)	HVT n = 20 (Me, lower-upper quartile)	*P*-level
hsCRP (mg/L)	3.17 (1.29-7.92)	1.5 (0.43-4.12)	<.01
PBFA (ng/mL)	0.16 (0.097-0.19)	0.18 (0.14-0.2)	NS
TFN-α (pg/mL)	2.43 (1.92-3.83)	1.16 (0.23-1.2)	<.01
IL-1β (pg/mL)	2.20 (1.57-3.83)	1.80 (0.95-2.19)	<.01
IL-6 (pg/mL)	1.87 (1.39-2.57)	1.50 (0.45-1.91)	<.01
IL-8 (pg/mL)	5.42 (3.21-8.12)	3.38 (2.45-4.10)	<.01
IL-10 (pg/mL)	2.53 (0.96-3.56)	1.84 (0.94-2.51)	NS
Neopterin (nmol/L)	11.49 (10.28-14.31)	9.15 (5.57-10.78)	<.01
	Patient with IsAF n = 70 (Me, lower-upper quartile)	**Normal values**	
PRA (ng/mL/h)	2.45 (0.1-2.92)	0.7-3.5	—
Aldosterone (pg/mL)	81.7 (25.18-117.8)	30-355	—

3.2 | EMB results

According to EMB, despite the absence of clinical and laboratory-instrumental signs of myocarditis, in 29% (28 persons) of patients, a lymphocytic myocarditis (Figure 1A) was revealed histologically and in 71% (68 people)—fibrosis (Figure 1B). Immunohistochemical assay defined the presence of antigens to various cardiotropic viruses in the myocardium of 42 patients (43.8%), regardless of the myocarditis histological signs presence: antigens to herpes simplex virus type 1 and type 2 were found in 20, to enterovirus VP-1—in 9, to cytomegalovirus—in 8, adenovirus in 3, parvovirus B19—in 2 examined persons.

In order to determine the possible relationship between the increasing of plasma inflammatory markers and myocardial inflammation, patients of the study group were divided into subgroups according to the results of EMB and immunohistochemical assay: "Patients with AF and myocarditis" (subgroup 1) and "Patients with AF and fibrosis" (subgroup 2), «Virus positive» (subgroup 3) and «Virus negative» (subgroup 4).

3.3 | Analysis of inflammatory markers in subgroups

The results of subgroup 1 and 2 comparison are presented in Table 3, where it can be seen that IL-6 was the only cytokine whose level at "Patients with AF and myocarditis" was significantly higher than that in "Patients with AF and fibrosis" and the HVT. The subsequent ROC analysis (Figure 2) showed that when the concentration of serum IL-6 > 1.6 pg/mL (Cutoff Value), the sensitivity of this marker in the diagnosis of latent inflammation in patients with IsAF is 75%, specificity 75% at $P < .01$.

We also compared levels of inflammatory markers in «Virus positive» and «Virus negative» subgroups and revealed significance differences only in neopterin (Table 4, Figure 3).

ROC analysis showed following level values: for neopterin sensitivity was 51%, specificity—84% (AUC = 0.675, cutoff value > 13.2 nmol/L, $P < .01$); (Figure 4). So, neopterin showed low sensitivity, but good specificity.

4 | DISCUSSION

Atrial fibrillation is the most common form of supraventricular arrhythmia and is associated with the development of various thromboembolic complications. In most of the cases, AF is attributable to other cardiovascular disorders such as hypertension, heart failure, and CAD.[2] The role of inflammation in the pathogenesis of IsAF remains equivocal and limited.

The study of Frustaci et al[12] revealed histological signs of inflammation at atrial histology in most of the patients (66%) with paroxysmal idiopathic AF refractory to conventional antiarrhythmic therapy.

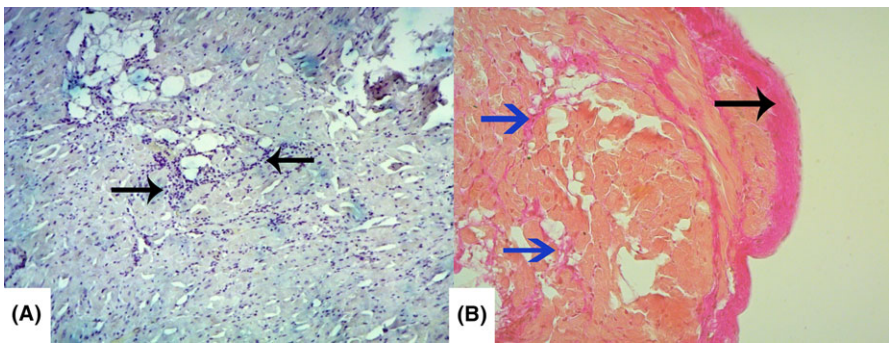

FIGURE 1 A, B, Histology of endomyocardial biopsies of patients with AF. A, Diffuse lymphocytic myocarditis (lymphocytes infiltrate is marked with arrows). B, Myocardial fibrosis. Connective tissue (Van Giesonstain), black arrow—endocardial fibrosis, blue arrows—interstitial fibrosis

TABLE 3 Levels of plasma inflammatory markers in subgroups, defined according to EMB results of patient with IsAF

Marker 1	Patients with AF and myocarditis (subgroup 1) (n = 28) (Me, lower-upper quartile) 2	Patients with AF and fibrosis (subgroup 2) (n = 68) (Me, lower-upper quartile) 3	*P*-level, Mann-Whitney test 4
neopterin (nmol/L)	11.57 (10.45-13.2)	13.25 (9.16-14.31)	<.01
TNF-α (pg/mL)	2.66 (1.87-3.16)	2.61 (1.92-3.83)	NS
IL 1β (pg/mL)	2.51 (1.92-3.39)	2.36 (1.57-2.96)	NS
IL-6 (pg/mL)	2.51 (1.62-2.71)	1.91 (1.33-2.56)	<.01
IL-8 (pg/mL)	7.12 (4.8-11.7)	5.47 (3.2-8.2)	<.01
hsCRP (mg/L)	5.67 (2.07-9.8)	4.16 (1.19-6.74)	NS

NS, not significant.

In several studies, the association of inflammation markers and AF occurrence was demonstrated.[13,14] Conversely, other investigators failed to show inflammatory changes in left atrium histological specimens from lone AF patients.[15]

In the presented study, a lymphocytic or polymorphic cell myocarditis was revealed by EMB in 29% (28) patients with IsAF. Immunohistochemical assay defined the presence of antigens to various cardiotropic viruses in the myocardium of 43.8% (42) patients, regardless of the myocarditis histological signs. These results suggest latent virus carrying in 56.2% patients of studied group. Similar facts were published earlier.[16,17] However, the role of the presence of a latent virus infection in the myocardium in the development and maintenance of AF is unclear.

It should be noted that in present study, histological findings were derived from biopsy of right ventricle (RV) and the inflammatory substrate in atria was not directly proved. However, we could assume its presence considering the results of the study of Begieneman et al[18], which showed that ventricular myocarditis as a rule coincides with atrial myocarditis. In any case, to confirm myocarditis in patients with AF, the EMB should be done. However, myocardial sampling of atria is dangerous due to very thin walls and EMB usually performed through access to the RV.[19] Nevertheless, this procedure is connected with risk of acute complications and indications for EMB are limited.[20,21] Thus, it is important to develop new noninvasive methods for diagnostics of inflammatory injury in myocardium, which will allow expanding indications for EMB. The detection of specific blood markers of latent myocarditis is one of the promising approaches to the solution of the problem mentioned above, and researchers around the world are actively studying this issue.

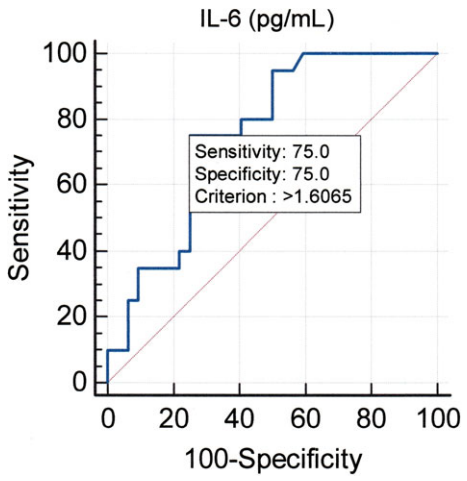

FIGURE 2 Plasma IL-6 level values receiver-operator characteristic (ROC) curve in patients with IsAF and myocarditis according to the results EMB. Area under the curve is 0.759 ($P < .01$). For a cutoff value of 1.6 pg/mL, the sensitivity was 75%, and the specificity 75%

In this present study, the concentrations of all plasma inflammatory markers in the blood were significantly higher in the group of patients with persistent IsAF than in the HVT group. This indicates the development of a systemic inflammatory response to stress associated with prolonged arrhythmia and hemodynamic disorders.[6] Similar results were obtained by other authors who analyzed plasma inflammatory markers in patients with AF, complicated with CAD and/or other cardiac pathology.[9]

Particularly, we found higher concentrations of hsCRP in patients with AF in comparison with the HVT. Among all biochemical markers of inflammation, it is the most studied and, to date, associated with a number of life-threatening cardiovascular events.[22] The true mechanism for increasing the content of hsCRP in peripheral blood during AF paroxysms remains unknown. It is suggested that this is due to an active local inflammatory reaction in the myocardium of the atria. It is also known that hsCRP is synthesized in response to increased production of IL-6 and IL-1β.[22]

Levels of neopterin (a metabolite formed as a result of biopterin biosynthesis) in the studied group were also increased, which indicates an activation of an oxidative stress and a cellular immune response associated with the inflammatory process.[23] In many other studies, similar results were obtained in patients with AF associated with other cardiovascular disease.[23,24]

In our work, it was no difference at the level of anti-inflammatory IL-10 between studied and HVT groups. In the world literature, there is only a single data on the level of this cytokine in patients with AF, which also demonstrated the absence of differences with the comparison group.[25,26]

TABLE 4 Levels of plasma neopterin in «Virus positive» and «Virus negative» subgroups in patient with IsAF

Marker	«Virus positive» (subgroup 3) (n = 42) (Me, lower-upper quartile)	«Virus negative» (subgroup 4) (n = 54) (Me, lower-upper quartile)	*P*-level, Mann-Whitney test
neopterin (nmol/L)	14.69 (10.45-15.8)	12.16 (9.16-13.08)	<.01
TNF-α (pg/mL)	3.06 (1.92-3.83)	2.72 (0.72-3.28)	NS
IL 1β (pg/mL)	2.17 (1.56-3.09)	2.56 (1.56-3.02)	NS
IL-6 (pg/mL)	1.71 (1.5-2.51)	1.91 (1.41-2.64)	NS
IL-8 (pg/mL)	4.73 (3.93-8.12)	4.76 (2.02-6.36)	NS
hsCRP (mg/L)	5.12 (0.9-9.8)	3.69 (1.26-4.7)	NS

NS, not significant

To date, in many experimental and clinical studies, evidence has been obtained that RAS plays an important role in the ethiopathogenesis of AF, and the combination of pharmacological antagonists of RAS (ACEIs or ARBs) with antiarrhythmic therapy more significantly reduces the frequency of recurrence of this cardiac rhythm disturbance. However, this applies only to patients with associated arterial hypertension, heart failure and LV dysfunction,[4,5] and prophylactic efficacy of RAS antagonists for IsAF is not proved yet. Similarly, in the presented study, the RAS markers, in particular, the concentration of aldosterone and PRA in all patients of the study group was within the range of reference values. Our results are in a part consistent with the data of Erne et al[27] 2017, which showed that in patients with AF associated with hypertension, an increased concentration of plasma renin was detected 2 times more often than in patients with AF without concomitant hypertension (35.3% vs 16, 5%, $P = .005$). The aldosterone concentration between patients of these groups did not differ.[27]

Thus, the levels of inflammatory markers defined in a whole group of patients with IsAF showed a general inflammatory response to the stress associated with cardiac arrhythmia. Analogous results were previously demonstrated by other researchers.

In our work, an attempt to determine a specific plasma marker of latent myocarditis on the basis of an analysis of the EMB in this category of patients was performed for the first time.

It was shown that in the group of patients with AF and myocarditis diagnosed by EMB, the plasma IL-6 concentration significantly exceeds that in patients with AF without histological signs of myocardial inflammation and in the HVT group. The subsequent ROC analysis demonstrated a sufficiently high diagnostic efficiency of this marker (sensitivity 75%, specificity 75%) at values >1.6 pg/mL (Cutoff Value). There were no statistically significant differences in the concentrations of other cytokines.

It is known, that the proinflammatory cytokine IL-6 participates in the regulation of the acute phase of inflammatory response, stimulates the proliferation and differentiation of B and T cells, leukopoiesis and the synthesis of acute phase proteins in the liver. This cytokine is sensitive to induction from IL-1β and TNF-α.[8,9,28] To date, it has been shown that the concentration of IL-6 in the blood serum is increased at many inflammatory diseases, including myocarditis.[8,9,28,29]

In addition, we compared plasma markers between subgroups of patients with and without presence of immunohistochemical signs of the cardiotropic viruses persistence in the myocardium of patients with AF. The significance differences in plasma neopterin and IL-6 concentrations were established. The results of ROC analysis showed that at values >13.2 nmol/L neopterin has high specificity, but low sensitivity. The results of IL-6 diagnostic value were unsatisfactory.

For today it is known, that the main source of neopterin are monocytes, macrophages, dendritic cells, and endothelial cells

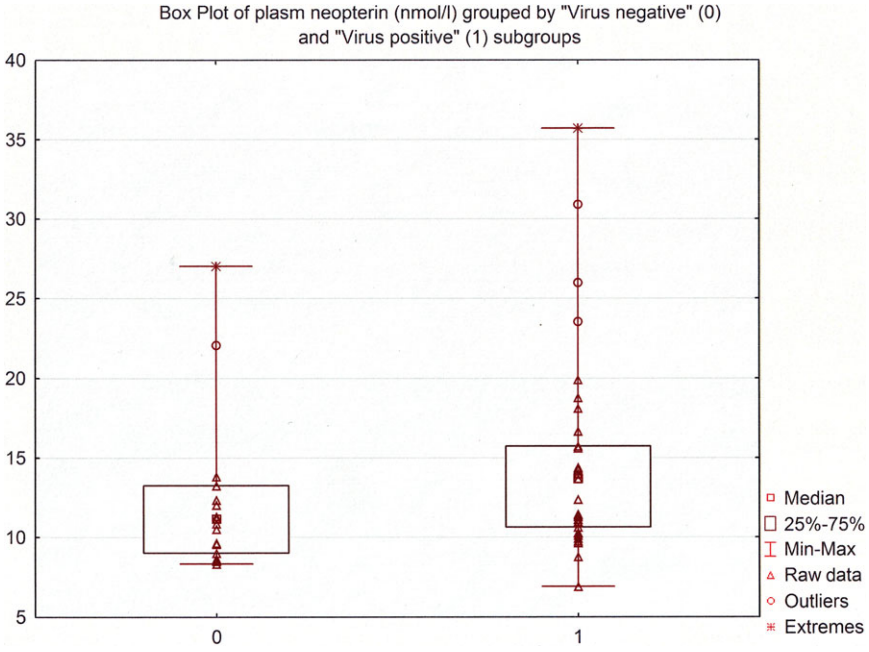

FIGURE 3 The plotted data of the levels of plasma neopterin (nmol/L) in "Virus negative" (0) and "Virus positive" (1) subgroups

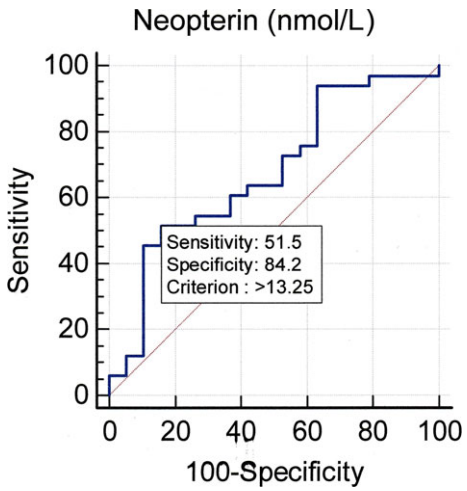

FIGURE 4 Plasma neopterin level values receiver-operator characteristic (ROC) curve in patients with IsAF and presence of cardiotropic virus antigens in myocardium according to the results EMB and immunohistochemistry assay. Area under the curve is 0.675 ($P < .01$). For a cutoff value of 13, 2 nmol/L, the sensitivity was 51% and the specificity 84%

activated by IFN-γ. The amount of synthesized neopterin is directly proportional to the amount of IFN-γ, and also indirectly indicates an increase in IFN-α. To date, the dependence of this marker concentration increasing on the progression of viral infections has been shown.[30–32] In this regard, the evaluation of neopterin activity in the blood can be a useful test for estimation of the immune and metabolic processes dynamics at viral myocarditis. Definition of this marker level may possibly allow to monitor the effectiveness of antiviral therapy or to suspect a latent myocardial inflammation in AF or other arrhythmias of unclear etiology, which, however, requires further study.

The majority of questions regarding upstream therapy of atrial fibrillation, in particular the possibility to use the myocardial inflammation and viral persistence as therapeutic targets, are still without answers. After myocarditis verification, the choice of possible treatment is made on the base of both guidelines for diagnosis and treatment of myocarditis[20] and guidelines for the management of patients with atrial fibrillation.[1] It has been reported that chronic myocarditis should be treated depending on the pathogenesis, such as viral infection or autoimmunity. However, the effectiveness of immunosuppressant and NSAID has not been confirmed.[20] Only some cases of specific myocarditis may respond to corticosteroid treatment. There are also few publications showing the ability of periprocedural steroid therapy to reduce AF early recurrence after catheter ablation.[33,34] It is possible to perform specific antiviral treatment if polymerase chain reaction (PCR) will identify the genomes of viruses in myocardium samples.[20] Treatment with angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers are usually performed to protect the myocardium.[1,20] Thus, the key role for a choice of specific medication still plays the EMB results. All the other noninvasive tools, including blood markers, may serve only as additional methods for selecting patients with idiopathic AF for EMB procedure.

5 | CONCLUSION

In this work, it was shown that in patients with IsAF the plasma levels of TNF-α, IL-1ß, IL-6, IL-8, neopterin, and hsCRP exceeded that in comparison with healthy volunteers, while the concentration of IL-10 did not differ. Markers of RAS, particularly PRA and aldosterone concentration, were within the range of reference values.

According to EMB data and immunohistochemical examination of endomyocardial samples, lymphocytic myocarditis was diagnosed in 29%, and signs of persistence of viruses in the myocardium in 43.8% of patients with IsAF.

In this study, a specific serum marker of the latent myocarditis in patients with AF was IL-6 at a concentration of more than 1.6 pg/mL, and the marker of latent viral myocardial infection was neopterin at concentrations >13.2 nmol/L. The increased levels of these markers can serve as a sign of latent viral myocarditis in AF of unclear etiology.

CONFLICT OF INTERESTS

Authors declare no Conflict of Interests for this article

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