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Cytokine Interleukin-6 in Patients with Paroxysmal Atrial Fibrillation

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Abstract*: **Introduction: Interleukin 6 (IL-6) is a major cytokine with an important role in the inflammatory cascade. There has been a growing body of evidence in recent years of the role of inflammatory cytokines in atrial fibrillation (AF), although the studies in this field have been inconclusive. Objective: To find changes in IL-6 that correlate with paroxysmal atrial fibrillation (PAF), and study in dynamics the plasma concentrations of this cytokine. Materials and methods: Plasma concentrations of IL-6 were measured three times in 51 patients (26 men and 25 women; mean age 59.84 ± 1.60 yrs) with paroxysmal atrial fibrillation (PAF): once immediately after hospitalization of these patients (that is, during the rhythm disorder episode at baseline), then at 24 hours and finally 28 days after restoration of sinus rhythm. The plasma concentration was measured only once in the control group of 52 patients (26 men, 26 women; mean age 59.50 ± 1.46 yrs). We used ELISA kit to determine the IL-6 concentrations in plasma. The sinus rhythm was restored with propafenone for all patients. Results: All patients were hospitalized between 2 and 24 hours after onset of arrhythmia (mean duration of AF episodes until hospitalization was 8.14 ± 0.76 hours). Baseline plasma concentrations of IL-6 were higher than those of controls (29.88 ± 1.68 vs 14.21 ± 0.50 pg/mL, P< 0.001). The difference was retained for 24 hours after sinus rhythm restoration of (26.84 ± 1.11 vs 14.21 ± 0.50 pg/mL, P< 0.001). At 28 days there was no statistically significant difference between patients and controls (16.03 ± 0.90 vs 14.21 ± 0.50 pg/mL Hb, P=0.08). Conclusion: IL-6 was measured very soon after the onset of paroxysmal atrial fibrillation. Its concentration levels in plasma were significantly elevated and decreased slowly after restoration of sinus rhythm. The changes we found provide a strong rationale to suggest that they are most likely associated with the intimate mechanisms of the disease. This in turn raises the question about the need for developing new therapeutic approaches to PAF.**

Keywords: interleukin 6, dynamics, atrial fibrillation, sinus rhythm

1. Introduction

Cytokines, which are essentially either proteins or glycoproteins, include a plethora of interleukins, interferons, colony-stimulating factors and a lot of growth factors. They are multifunctional, even including opposing functions, which sometimes is determined solely by the cytokine levels [1]. Interleukin 6 (IL-6) is a typical representative of this class of substances [2].

IL-6 is 22-27 kDa polypeptide secreted from not only a number of immune cells such as activated monocytes, macrophages, etc, but also from some cardiovascular components such as endothelial cells, vascular smooth muscle cells and fibroblasts in response to various stimuli such as TNF-α, IL-1β, oxidative stress, etc [3], [4]. Unlike many other cytokines that function via paracrine or autocrine mechanisms the major effects that IL-6 exerts are a direct consequence of its concentration in the circulation. IL-6 was first described in 1980 as interferon-β-like protein but our understanding of its role in a number of physiological and pathophysiological processes today has dramatically changed. IL-6 is actually a soluble mediator with pleiotropic effects. Typically, it elevates its levels promptly and transiently in response to tissue injuries, incl. immune response, excessive cellular growth and hemostatic dysbalance [5]. IL-6 is also well recognized as a primary cytokine in the inflammatory cascade. It participates in the acute phase of inflammation, and in generating and propagating chronic inflammation [6]. For a long time it has been considered to be a prototype of proinflammatory cytokines involved in the pathogenesis of many, and maybe of all, inflammatory diseases. It has been found recently that IL-6 has also anti-inflammatory properties. This capacity of IL-6 to display both pro- and anti-inflammatory properties is thought to be a result of the activation of different signalling pathways [7]. IL-6 gets involved in the inflammatory processes by activation and proliferation of lymphocytes, differentiation of B cells, leukocyte recruitment and induction of acute-phase response in the liver [8]. IL-6 is considered to be a major regulator of the inflammatory process.

AF is the most common arrhythmia in clinical practice – the condition affects between 0.4% and 1% of the general population [9], [10]. Epidemiological studies have estimated that PAF constitute between 25% to 60% of all AF cases - its

recurrences are associated with structural and electrical remodelling of the myocardium [11]. The pathophysiologic nature of this condition is complex and still poorly understood - a solid proof of this fact is the failure of the anti-relapsing treatment. In recent years, a great body of evidence has been amassed about the role of inflammatory cytokines in AF, and yet the results are still ambiguous and inconclusive [12]-[16]. Therefore AF-related IL-6 behavior rouses considerable scientific interest.

2. Aim

To find changes in IL-6 associated with AF manifestation and measure plasma concentrations of this cytokine in dynamics.

3. Materials and methods

3.1 Study design

The study was conducted in the Intensive Cardiac Unit of St. Marina Hospital, Varna in Bulgaria between October 2010 and May 2012 after obtaining approval by the Hospital Research Ethics Committee (No 35/29.10.2010) and in accordance with the Helsinki Declaration [17]. The participants were enrolled in the study after obtaining a written informed consent from them. We measured the IL-6 plasma concentration in patients with paroxysmal atrial fibrillation (PAF). The measurements were performed three times: immediately after hospitalization of patients (that is, during the rhythm disorder which were the baseline values), at 24 hours and 28 days after restoration of sinus rhythm. The IL-6 concentration in plasma in the controls was measured only once.

Restoration of the sinus rhythm was achieved by administration of propafenone. The patients were discharged from hospital 24 hours later, and were followed up for 28 days after restoring the regular sinus rhythm. Control examinations were performed at days 7 and 24 after PAF termination. No AF recurrences were found in the careful taken medical history and in the ECG study we did after that.

3.2 Study population

We studied only PAF patients that had duration of arrhythmia less than 48 hours before hospitalization, when this arrhythmia episode might be terminated. The onset of the rhythm disorder was determined by taking a careful history in which patients could tell exactly when they started experiencing palpitation which lasted until hospitalization. A diagnosis of AF was made on the basis of ECG done immediately after patients were admitted into the hospital.

Out of a total of 338 patients, we selected only 56 (31 men, 22 women) that had their sinus rhythm restored and maintained regular until the end of study. Two hundred and eighty-two patients with PAF were dropped out of the study on the basis of the exclusion criteria (see Exclusion Criteria).

To achieve a balanced gender distribution we selected subsequently 51 patients (26 men, 25 women) at the mean age of 59.84 ± 1.60 yrs (range 31-77 yrs).

The control group was composed using the same exclusion criteria (see Exclusion Criteria). Selection procedure of patients and controls aimed at eliminating and/or balancing to the greatest extent the two groups of factors that may have an impact on inflammation. This resulted in selecting only 52 controls out of a total of 169 screened subjects. Their mean age was 59.50 ± 1.46 yrs (range 30-76 yrs) as men and women were equal in number - 26 (50%). There was no pre-study evidence of AF in the histories and ECG studies of control.

Exclusion criteria.

1. Cardiovascular disorders including ischemic heart disease, heart failure, inflammatory or congenital heart diseases, moderate or severe acquired valvular diseases, cardiomyopathies.
2. Other diseases – renal, pulmonary or liver failure; diseases of the central nervous system; inflammatory and/or infectious diseases for the previous three months; neoplastic or autoimmune diseases; diseases of the endocrine nervous system (except for type 2 diabetes).
3. Hormone replacement therapy or use of contraceptives, pregnancy, systematic use of analgesics, incl. non-steroidal anti-inflammatory drugs, BMI > 35.
4. Persistence of the rhythm disorder after propafenone administration, rhythm regularization by electrical cardioversion, recurrence of AF until the end of the study (exclusion criteria for patients).

3.3 Blood samples and measurement of IL-6 concentrations

Plasma concentrations of IL-6 were determined in venous blood sample taken in heparin vacutainer tube (VACUETTE/4.0 ml/Li Hep). The blood samples were immediately centrifuged and the obtained plasma was frozen. Collecting and storing the blood samples was performed in accordance with the methodology used.

During the study the samples were never re-frozen.
Plasma concentrations of IL-6 were measured using an ELISA kit (Elabscience Biotechnology Co, Ltd, China) in compliance with the manufacturer's protocol. All measurements were done in duplicate. The coefficient of variation was <10%.

3.4 Propafenone regimen

Propafenone was administered as 2 mg/kg iv bolus, by infusion at a dose of 0.0078 mg/kg/min for 120 min and then as p.o. intake in a dose of 300 mg TID at an interval of 8 hours [18], [19]. This regimen continued for 24 hours. After restoring the sinus rhythm the regimen was discontinued and all patients received propafenone in a maintenance dose of 150 mg TID until the end of the study.

3.5 Statistical analysis

Descriptive statistics was used to calculate the means, relative proportions and the central tendency (Mo). The Student's t-criterion was used to test the hypotheses of equality of means and of relative proportion. $P < 0.05$ was considered statistically

significant. The analysis of all data was carried out with a specialized statistical analysis package (GraphPad PRISM, Version 5.00). The results were presented as mean ± SEM or n (%).

4. Results

4.1 Clinical characteristics of participants

There was no statistically significant difference between patients and control group in their demographic characteristics, concomitant diseases and the therapy to treat them (P >0.05) (Table 1). The groups did not differ statistically significantly in terms of harmful habits, body mass index and ultrasound characteristic (P >0.05) (Table 1).

The analysis showed that the mean duration of AF until hospitalization was 8.14 ± 0.76 hours. All 51 patients were hospitalized between 2 hours and 24 hours after onset of arrhythmia, but most frequently it was done at 5 hours (Mo = 5; 10 of all 51 patients).

	PAF Patients	Controls	P
Number	51	52	P= 0.89
Mean age (years)	59.84±1.60	59.50±1.46	P= 0.87
Men/Women	26/25	26/26	P=1/P= 0.93
Accompanying diseases			
Hypertension	37 (72.54%)	34 (65.38%)	P= 0.44
Type 2 Diabetes mellitus	3 (5.88%)	2 (3.84%)	P= 0.62
Chronic ulcer disease	2 (3.92%)	0	P= 0.15
Status post hysterectomy	2 (3.92%)	1 (1.92%)	P= 0.54
Benign prostatic hypertrophy	1 (1.96%)	0	P= 0.32
Dyslipidemia	4 (7.84%)	3 (5.77%)	P= 0.69
Medication for hypertension and dyslipidemia			
Beta blockers	19 (37.25%)	17 (32.69%)	P= 0.62
ACE inhibitors	15 (29.41%)	14 (26.92%)	P= 0.78
Sartans	11 (21.57%)	9 (17.31%)	P= 0.58
Statins	4 (7.84%)	3 (5.77%)	P= 0.69
Harmful habits			
Smoking	8(15.69%)	7(13.46%)	P= 0.75
Alcohol intake	7(13.72%)	6(11.53%)	P= 0.74
BMI (kg/m^2)	23.85±0.46	24.95±0.45	P= 0.09
Ultrasound study*			
LVEDD (mm)	52.57±0.58	52.29±0.57	P= 0.73
LVESD (mm)	34.43±0.56	34.73±0.48	P= 0.69
EF (%)	62.98±0.70	61.54±0.58	P= 0.12
IVS (mm)	10.37±0.23	9.92±0.26	P= 0.20
PW (mm)	10.24±0.21	9.73±0.28	P= 0.16
LA volume (ml/m^2)	22.81±0.45	23.82±0.48	P= 0.13
RVEDD (mm)	30.54±1.58	29.17±1.52	P= 0.18

Table 1. Characteristics of patients and controls

LVEDD – left ventricle end-diastolic diameter; LVESD – left ventricle end-systolic diameter; EF – ejection fraction; IVS –interventricular septum; PW – posterior wall; LA volume – left atrium volume; RVEDD – right ventricle end-diastolic diameter

4.2 IL-6 plasma concentrations

Figure 1 shows the changes in IL-6 plasma concentrations, which at baseline (at admission to hospital) were higher than those of the controls (29.88 ± 1.68 vs. 14.21 ± 0.50 pg/mL, P<0.001). This difference was kept at 24 hours after sinus rhythm restoration (26.84 ± 1.11 vs 14.21 ± 0.50 pg/mL, P< .001). Twenty-eight days after restoration of sinus rhythm there was no significant difference from the controls (16.03 ± 0.90 vs 14.21 ± 0.50 pg/mL Hb, P = 0.08).

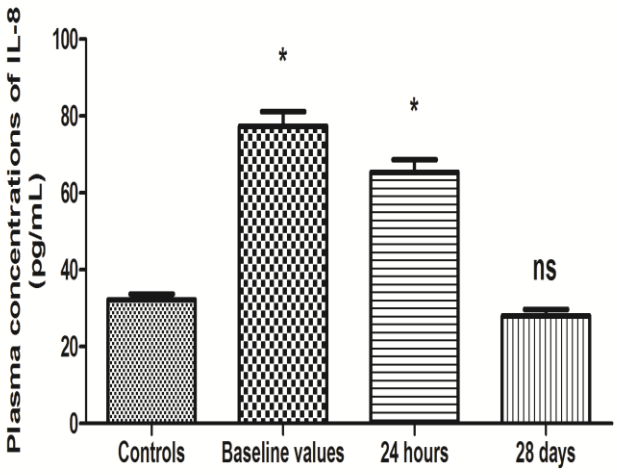

Figure 1. Dynamics of IL-6 plasma concentrations (pg/mL) in PAF.
(baseline values – upon patients' hospitalization; 24 hours – 24 hours after rhythm regularization; 28 days - 28 days after rhythm regularization; *- P< 0.001; ns – statistically insignificant difference).

5. Discussion

IL-6 is one of the primary inflammatory mediated cytokines that determines to a great extent what the inflammatory response will be [20]. The changes this cytokine undergoes in AF occurrence are the subject of numerous studies. A meta-analysis of 99 studies has shown that IL-6 circulating levels in AF are significantly higher than those of controls [21]. Another important finding in this analysis is the fact that AF recurrence after electrical cardioversion or catheter ablation as well as postoperative AF could be predicted by the increased levels of IL-6.

Although there are a great number of studies on the changes of the cytokine in AF, researchers are predominantly interested in the persistent and permanent AF – this marker is most often studied in populations with high disease burden which also bears upon the inflammatory profile [22, 23, 24]. Sata et al studied this interleukin also in PAF, but the follow-up after restoration of sinus rhythm was short and did not allow determining the nature of the changes [25]. In view of the facts we have given above, it is worth noting that in the present study the plasma concentrations of IL-6 were measured extremely early (within 24 hours of the clinical onset of PAF – the baseline values) and were followed up for a long period of time (28 days) after regularization of the sinus rhythm. It is the early determination of this marker that makes it possible to find how it correlates to PAF manifestation and this in turn would open up new opportunities in the therapeutic approach to the disease. The statistical analysis we made showed that the baseline values of IL-6 were significantly higher when compared with those of the controls (P< 0.001) (Figure 1). It is well known that this cytokine is an established index of inflammation [26]. Hence we can assume that PAF, even in the very early hours of occurrence (within 24 hours), can be characterized by an increased inflammatory activity. Moreover, it is precisely its elevated concentration levels measured very soon after the onset of PAF that provide a reason to assume that they are not accidental findings. Most likely, there is a strong correlation

between IL-6 plasma concentration and the rhythm disorder. The mechanisms involved in the onset, sustainment and recurrence of AF have been in the focus of research interest since the beginning of the last century, when the multiple wavelet hypothesis was put forward for the first time [27, 28]. It has been recognised now that to develop and sustain, AF needs both a trigger and a suitable substrate [21]. Ectopic activity is a possible trigger causing rhythm disorders while the electrical and structural remodelling is recognised as the primary substrate for the disorder to sustain and relapse [29, 30]. The role of IL-6, and hence of the inflammatory process in the complex relationship of a trigger and substrate is not yet fully understood. Mitrokhin et al have demonstrated that elevation of IL-6 levels result in electrophysiological changes of atrial myocardium, which facilitates the onset of AF [31]. That is why it is of paramount importance to measure the IL-6 levels not only during an AF event but also while there is sinus rhythm. The present study showed that IL-6 plasma concentration remain significantly elevated 24 hours after termination of arrhythmia ($P < 0.001$) (Figure 1). This finding is extremely important. It shows that the inflammatory activity is enhanced not only during AF, but also with the sinus rhythm restored. It is thus logical to assume that its effect on the body, and in particular on the atrial myocardium, is also sustained. Twenty-eight days after sinus rhythm was restored, we found no statistically significant difference in the measured concentrations of IL-6 between patients and controls ($P = 0.05$) (Fig. 1). With the termination of arrhythmia the concentrations of IL-6 decrease. This implies also a decrease of the inflammatory activity in the body, although it occurs slowly. Summing up the results we could conclude that studying IL-6 plasma concentrations first during an AF event and then during sinus rhythm has serious advantages. Studying them in dynamics allows us the opportunity to determine the nature of the changes we find and also find what their impact is on the clinical manifestation of the disease. It becomes clear that the elevated levels of IL-6 concentrations and the consequences they cause in PAF are not a one-stage event in the course of the disease. This raises a very important question about the plasma concentrations of the marker prior to the onset of the rhythm disorder. The answer to this question will throw light on whether the changes in the cytokine precede the development of arrhythmia or are a result of it. For the purpose, however, the study design should be different from that we used in the present study.

6. Conclusion

IL- 6 was studied very soon (between 2 and 24 hours) after the onset of paroxysmal atrial fibrillation. Its concentration levels in plasma were significantly elevated and decreased slowly after restoration of sinus rhythm. The changes we found provide a strong rationale to suggest that they are most likely associated with the intimate mechanisms of the disease. This in turn raises the question about the need for developing new therapeutic approaches to PAF

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Competing interests
Authors have declared that no competing interests exist.

Informed Consent
All authors declare that written informed consent was obtained from all participants of the study. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal.

Ethical approval
The study was approved by the Ethics Committee of Scientific Research (№35/29.10.2010) at St. Marina Hospital, Varna and was also performed in compliance with the Declaration of Helsinki.

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