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New Units in the Pathogenesis of Atrial Fibrillation in Patients with CHD and Hypertension

N.E. Grigoriadi, N.S. Karpunina, L.M. Vasilez, A.V. Tuev, O.V. Chlynova, A.A. Krivaya and A.V. Petrusha

Perm State Medical Academy of a name of academician E.A. Wagner, Perm, Russia

Abstract: We studied C-reactive protein (CRP) and cytokine spectrum: tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-17 (IL-17) in patients with coronary heart disease (CHD), hypertension (H), with persistent form of atrial fibrillation (PAF) and without cardiac arrhythmias. Al the studied markers of inflammation: CRP, TNF-α, IL-1β, IL-6, and especially IL-17 has a predictive value in the development of PAF. In patients with hypertension (H) combined with atrial fibrillation (AF), the paroxysmal AF is associated with a significant increase in the concentration of TNF-α, but the level of CRP is inversely correlated with the severity of arrhythmia. The study confirms the involvement of inflammation in the pathogenesis of atrial fibrillation in patients with CHD and hypertension.

Key words: Atrial fibrillation · Arterial hypertension · Ischemic heart disease · C-reactive protein · Tumor necrosis factor alpha · Interleukins 1β · 6 · 17 · Prediction

INTRODUCTION

AF is still a serious and unsolved problem for practicing doctors and researchers. As pathogenic mechanisms, we consider acute or chronic hemodynamic, metabolic and inflammatory processes [1]. All of them can lead to structural remodeling of atria, which leads to the development and progresses of AF. Several studies indicate the inflammatory theory of the pathogenesis of AF [2-5].

In 2001, the results of the first documented clinical study were published; this study demonstrated a high level of CRP in patients with AF compared with those with normal sinus rhythm [6].

Naoyuki Sata, *et al.* found that the level of CRP, IL-6 and tumor necrosis factor-alpha were significantly higher in patients with paroxysmal and persistent forms of AF against the background of various organic heart disease, than in the control group ; their concentration were significantly higher in the constant form of AF. This hypothesis is confirmed by other studies [9].

The above data have defined the purpose of the study.

Objective: To study the parameters of immune inflammation in atrial fibrillation in patients with hypertension and coronary heart disease, to identify the predictive value of inflammatory factors in the occurrence of arrhythmias in patients with ischemic heart disease and hypertension.

MATERIALS AND METHODS

The study involved 200 patients, of whom 72 patients with CHD, 97 - with hypertension. The comparison group included 31 apparently healthy people. All groups were comparable in age and sex.

The criteria of exclusion from the study were: cardiac rhythm disorders in the type of frequent (more than 30 per hour) ventricular extrasystole (B.Lown classification), ventricular tachycardia , cardiac failure more than II functional class NYHA; secondary (verified) hypertensive syndrome , creatinine of more than 150 micromole/l, diabetes mellitus type 1 and type 2 , glucose tolerance disturbance , bronchial asthma; not coronary heart disease (cardiomyopathy , myocarditis) , heart ailments , thyroid dysfunction , acute inflammatory diseases or

Corresponding Author: Grigoriadi, Perm State Medical Academy of a name of academician E.A. Wagner, Perm, Russia.

chronic inflammatory disease exacerbation during 2 weeks prior to study entry.

All the patients were examined clinically and using a special complex of methods to assess the structural and functional state of the myocardium, heart rate variability, blood pressure variability and indicators of inflammation.

We determined the levels of inflammation indicators: CRP (an indicator of systemic inflammations) and TNF - alpha (an indicator of local inflammation of the myocardium). We used the method of enzyme-linked immunosorbent assay using the standard test systems: "DSL-10-42100" series 07144-A, "Biokhimmak" Ltd (Moscow) - for CRP, and "ProConTNFα" code K020 "Protein contour" Ltd (St. Petersburg, Russia) - for TNF-alpha.

Daily blood pressure monitoring was conducted in accordance with the directions of the Joint National Committee on Treatment of High Blood Pressure, 1997. (Acute Circulatory Problem VI, 1997). Measurements were made at intervals of 15 minutes during the day (during wakefulness of the patients) and at intervals of 30 minutes during the night (during sleep), followed by calculation of mean values of systolic and diastolic blood pressures per day during wakefulness and sleep[10]. We used portable recorders manufactured by «Astrocard», data analysis was performed using the program BPLab on a compatible PC.

Long-term monitoring of ECG (LM ECG) was made to all the studied patients. We used portable cardio recorders manufactured by «Brentwood» company, USA, with a continuous 24 - hour ECG recording and subsequent automated analysis on the IBM PC - compatible computer, the RhythmScan 8800 Precision program [11].

The received results were statistically processed by a computer program Statistica 6,0. Quantitative indicators with normal distribution are presented as M ± σ (mean ± standard deviation). To identify the existing differences in the sequence features we used the nonparametric Mann-Whitney criteria. In multiple comparisons we used the method of dispersion analysis of Kruskal-Wallis test (detection of differences in the aggregate of groups, if their number is exceeds 2). The correlation analysis was performed using Spearman's R criteria for quantitative values. When $p < 0.05$ the differences were considered as statistically significant. The effectiveness of diagnostic tests, in particular CRP and TNFα in point of such nosology as atrial fibrillation, was conducted on the following parameters: sensitivity (Se), specificity (Sp), positive predictive value (PVP), negative predictive value (PVN), the index of diagnostic efficiency (IDE), the separation point, a priori chances, posterior chances.

The study design is presented as an open-controlled study.

RESULTS AND DISCUSSION

The relatively stable CHD, namely angina pectoris, characterized the average content of pro-inflammatory cytokines with an appropriate correlation between the production of IL-6 and CRP (Tab.1).

The CRP level in the multifactorial regression analysis, CRP acted as an independent predictor of heart failure (HF).

All the inflammatory markers: CRP (Beta = 0,569, p = 0, 04), TNF-α (Beta = 0,506, p = 0, 00), IL-1β (Beta = 0,268, p = 0.00), IL-6 (Beta = 0,370, p = 0.0008) have a predictive value in the development of persistent form of atrial fibrillation PAF. In a multifactorial regression analysis, only CRP (Beta = 0,323, p = 0,048) maintained an independent prognostic value.

We got a separation point 2.6 mg / l for CRP, the excess of which was considered as a sufficient reason for the qualitative assessment of PAF risk (p = 0.001). The diagnostic efficiency for the value of 2.6 mg / L was the highest (0.54). The analyses of posterior chances showed a trend of increasing the risk of AF by the increasing of CRP levels: CRP rise from 2.6 to 5.7 mg / l was accompanied by an increase in the chance of developing of AF by 3.5 times.

The situation with TNF-α is similar. The separation point was 2.1 pg / ml (p = 0.02), at this level, we noticed an optimal ratio of sensitivity (68%) and specificity (72%) of this test, the IDE was 0.68. The TNF-α growth in the range of 2,1-4,1 pg / mL increased the risk of AF by 5 times. Separation point for IL-1β was 1.1 pg / ml (p = 0.0001). The diagnostic efficacy of the test for this value was 0.53. The increasing concentrations of IL-1β from 0.9 to 1.3 pg / mL was attended with an increased risk of AF by 3 times. For IL-6 the separation point is - 3.0 pg / ml (p = 0.003), IDE for this value is- 0.41. We also defined a twofold increase of the risk of AF when the concentration of IL-6 increases, especially in two ranges - from 2.1 to 2.3 and from 3.1 to 3.4 pg / ml.

Long since it has been assumed that atrial fibrillation-an attribute of fibrous or degenerative changes in the atrial myocardium, the sinus node and / or conductive ways, and the initial cardiac disease was considered as a

Table 1: Characteristic of the cytokine spectrum indicators in the studied groups

Parameters	CRP, mg/l	TNF-α, pg/ml	IL-1β, pg/ml	IL-6, pg/ml	IL-17, pg/ml	IL-4, pg/ml
HF II-III functional class, (N=32) M±δ	3,7±1,90	4,3±6,18	1,9±1,80	6,2±4,17	0,02±0,06	1,9±2,23
PAF + CHD, (N=40) M±δ	3,8±2,02	4,1±3,16	1,5±0,96	5,9±3,79	8,7±9,53	2,2±3,61
Control (N=33), M±δ	1,6±1,27	1,0±1,74	0,8±1,46	3,0±3,82	1,5±5,52	1,8±1,12

$\delta_{1\text{-}3}$=0,000001 (CRP), =0,0002 (TNF-α), =0,001 (IL-1β), =0,00001 (IL-6);

$\delta_{2\text{-}3}$=0,000001 (CRP), =0,00 (TNF-α), =0,0001 (IL-1β), =0,00002 (IL-6);

Table 2: Comparative characteristics of immune inflammation indicators in patients with hypertension

	permanent form of AF (N=17)–1gr.	*paroxysmal form of AF out of the fibrillation paroxysm* (N=20)-2gr.	*AH* (N=42)-3 gr.	*paroxysmal form of AF during the fibrillation paroxysm* (N=18)– 4gr.	*Healthy people* (N=22)–5gr.	P
TNF,Pkg/ml						
(M±σ)	14,81±1,77	14,21±6,61	17,96±13,78	389,06±191,02	1,16±0,64	$P^{1\text{-}5}$=0,0001*
						$P^{1\text{-}2}$>0,05**
						$P^{1\text{-}3}$>0,05**
						$P^{2\text{-}3}$>0,05**
						$P^{2\text{-}4}$=0,0001**
						$P^{3\text{-}5}$=0,0001**
CRP, mg/l						
(M±σ)	2,76±0,22	4,69±2,14	4,99±1,82	5,72±2,65	1,36±0,71	$P^{1\text{-}5}$=0,0001*
						$P^{1\text{-}2}$>0,05**
						$P^{1\text{-}3}$=0,0038**
						$P^{2\text{-}3}$>0,05**
						$P^{2\text{-}4}$>0,05**
						$P^{3\text{-}5}$=0,0001**

Notes: * p <0.05 (Kruskal-Wallis criterion), ** p <0.05 (Mann-

recurrence. Inflammation - the cause or a consequence of atrial fibrillation? - The question remains open.

cause of these changes. However, at the present time, it became obvious that in addition to the classical theories of heart disease, hyperexpression of inflammatory factors can make a significant contribution: pro-inflammatory cytokines (IL-1, IL-6, IL-8, IL-12, TNF-alpha, interferon), CRP.

The characteristics of the CRP indicators and cytokine spectrum in patients included in the study, which reflect some of their inflammatory status, are presented in Table 1. Patients with hypertension unlike the comparison group, in general, had relatively higher values of proinflammatory cytokines that suggests the existence of a link between hypertension and inflammatory reaction involving a specific set of inflammation mediators.

Identifying the prognostic value of individual indicators in the development of hypertension, we marked out the following parameters: CRP (Beta = 0,264, p = 0,00), TNF-α (Beta = 0,282, p = 0,00). According to the multifactorial regression analysis, the same components maintained an independent predictive value, without reducing its predictive power (for CRP - Beta = 0,297, p = 0,00, for TNF-α - Beta = 0,291, p = 0.00), and outstripped the traditional risk factors again.

During the study, we got a reliable connection between the increase of TNF-alpha and the paroxysm of atrial fibrillation in patients with hypertension (Table 2). This cytokine was 7.5 times higher than the upper limit of normal, and is 25 times higher than in paroxysmal form out of paroxysm, and in constant form of AF, and 20 times higher than in the control group. These results suppose that the increased level of this cytokine is probably due to the launch of rate disruption in paroxysmal AF, which is confirmed by other studies data [6, 8, 9]. However, we do not have significant differences in the level of TNF -alpha in the permanent form, in the paroxysmal form of atrial fibrillation out of paroxysm, and in the comparison group. It is known that in the time of atrial fibrillation there is an electrical remodeling of the left atrium, which supports the persistence of arrhythmia [5]. Perhaps the significance of inflammation indicators plays an important role in the transformation of sinus rhythm into atrial fibrillation. It is possible that hyperexpression of TNF -alpha is a manifestation of arrhythmia's.

The results of our analyzes on forecasting is ascertainment of the fact of independent predictive values of infection, CRP and TNFα in respect of atrial fibrillation risk in patients with CHD and hypertension. Designation of separation points for quantitative tests will identify a group of patients with increased risk of cardiac arrhythmias.

CONCLUSION

- The consequence of inflammatory cytokines is reliably higher in patients with CHD than in the control group.
- In patients with hypertension, CRP and TNF-alpha concentrations were significantly higher than in healthy people.
- Paroxysm of atrial fibrillation is associated with a significant increase in the concentration of TNF-alpha. Changing the CRP concentration during the paroxysm of atrial has not been identified.
- CRP level is inversely correlated with the severity of atrial fibrillation, i.e. in persistent AF the markers of inflammation are lower than in paroxysmal AF in patients with hypertension without arrhythmias.

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