

Predictor Value Cytokines for Recurrence of Arrhythmia in Patients with Coronary Heart Disease Combined Hypertension and Persistent Atrial Fibrillation

E.V. Sid’

State Institute «Zaporizhzhia Medical Academy of Postgraduate Education of
Ministry of Health of Ukraine»

Copyright © 2014 E.V. Sid’. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract

Aim of the study was to determine the level of cytokines and Endothelin-1 in patients with coronary heart disease combined with hypertension and persistent atrial fibrillation and to establish the relationship between them in order to evaluate possible predictors of arrhythmia recurrence.

Methods: We examined 68 patients with coronary heart disease (CHD) combined with hypertension (HT) and persistent atrial fibrillation (AF) and 23 healthy persons aged from 45 to 65 years. Follow-up period was 18 weeks. Recurrence of atrial fibrillation has been reported in 25 patients.

Results: We found that in the group of patients with CHD combined with HT and persistent AF, there was a sharp significant increase in the concentration of interleukin-1 β (1.13 ± 0.12) PG/ml, interleukin-4 (0.75 ± 0.06) PG/ml, TNF-alpha (1.66 ± 0.24) PG/ml and endothelin-1 (3.96 ± 0.54) fmol/l in blood plasma in comparison with such indicators of healthy people. The conducted correlation analysis showed an average direct relationship between the level of IL-1 β and ET-

1 ($R = + 0.48$, with $p < 0.05$) and a strong direct relationship between the level of TNF- α and ET-1 $R = + 0.79$ ($p < 0.05$) in the group of patients.

Keywords: arrhythmia, atrial fibrillation, cytokines, endothelial dysfunction, inflammation

Introduction

Atrial fibrillation (AF) is one of the most common cardiac arrhythmia in clinical practice, which usually leads to disability. One-third of patients who are hospitalized for heart rhythm disturbance have AF. This type of arrhythmia worsens the prognosis of patient's survival, therefore the need for treatment it is out of doubt. Atrial fibrillation as a rule occurs in 1-1.5% of the general population and depends on age [1, 2]. It is interesting to study the occurrence of AF caused by mediators of inflammation and endothelial dysfunction in patients with coronary heart disease combined with hypertension [3].

Material and methods: Criteria for inclusion in the study: Male and female patients at the age from 45 to 65 years old; patients with persistent atrial fibrillation (PAF), II stage HT with mild-to-moderate BP, ischemic heart disease, angina of effort FC I-II or coronary arterial involvement (stenosis $> 50\%$). Known duration of such disease makes more than 6 months.

Criteria for exclusion from the study: Acute myocardial infarction; heart failure of the class higher than II according to NYHA Classification; diabetes mellitus, impaired glucose tolerance; bronchial asthma; cardiomyopathy, myocarditis; acute inflammatory diseases.

The patients with CHD combined with HT and persistent AF were included in the study during 24 hours after edema relapse of atrial fibrillation. We examined in total 68 patients with coronary heart disease combined with hypertension and persistent AF and 23 healthy persons aged from 45 to 65 years. Patients setting was conducted in the period from 2012 to 2013.

The main group consisted of patients with CHD combined with II stage HT and persistent AF, in total 68 persons of the average age of 58.8 ± 0.9 years. The second group of comparison consisted of 23 healthy people of the average age of 54.8 ± 1.1 years.

The level of Interleukin-1 β , Interleukin-4, tumor necrosis factor- α and Endothelin-1 in blood plasma was determined by ELISA method using standard sets IL-1 β -ELISA-best", "IL-4-ELISA-best", "TNF-alpha ELISA-best" (Vector-best, Russia) and ENDOFELIN reagents made by Biomedica (Germany) according to the method described in the application instruction for the test systems. The analysis was performed using "SUNRISE TS" (Austria) immunoassay analyzer.

The patients involved in the study received treatment according to the recommendations of ESC (2010). Some of the patients (33 persons) took Atovastatin (produced by KRKA Company) in the average daily dose of 20 mg, the remaining 35 patients refused statins, as they had a negative experience with the use of statins in history or a negative attitude to this class of drugs.

Statistical Analysis

The obtained data are presented as $M \pm m$ (where: **M** is arithmetic mean value, **m** is the arithmetic mean error) and **p-value** is specified at groups comparison. Difference at $p < 0.05$ was considered a reliable value. Logistic regression prediction model was estimated as an adequate and reliable Wald criterion (χ^2). Statistical processing of the obtained results was carried out using the methods of parametric and nonparametric statistics. For statistical data processing the statistical software package PSPP (version 0.7.9, license GNU GPL) was used.

Results and Discussion

The levels of cytokines and Endothelin-1 in the examined persons are presented in Table 1..

Table 1.. The levels of cytokines and Endothelin-1 in patients examined ($M \pm m$, $n = 71$)

Variable	The group surveyed persons	
	Persistent AF combined CHD and HT ($n = 68$)	Healthy people ($n = 23$)
	1	2
Interleukin-1 β , PG/ml P-value	1.13 ± 0.12 $p_{1-2} = 0.0001$	0.12 ± 0.03
Interleukin-4, PG/ml P-value	0.75 ± 0.06 $p_{1-2} = 0.003$	0.42 ± 0.06
FNO- α , PG/ml P-value	1.66 ± 0.24 $p_{1-2} = 0.0001$	0.20 ± 0.02
Endothelin-1, fmol/l P-value	3.96 ± 0.54 $p_{1-2} = 0.0001$	0.60 ± 0.06

In the group of patients with CHD combined with HT and persistent AF there was a sharp significant increase in the concentration of Interleukin-1 β , Interleukin-4, TNF-alpha and Endothelin-1 in blood plasma as compared with healthy people. The level of Interleukin-1 β (1.13 ± 0.12 PG/ml) in the group of patients with CHD combined with HT and persistent AF was higher in comparison with the level (of 0.12 ± 0.03 PG/ml) in the group of healthy people ($p < 0.05$).

A significantly increased level of Interleukin-4 (up to 0.75 ± 0.06 PG/ml) was observed in the group of patients in comparison with the level (of 0.42 ± 0.06 PG/ml) in the group of healthy people. FNO- α in the group of healthy people was at the level of 0.20 ± 0.02 PG/ml in comparison with the level of 1.66 ± 0.24 PG/ml in the group of patients with CHD combined with HT and persistent AF, with $p < 0.05$. The concentration of Endothelin-1 was significantly higher, in particular 6.6 times higher in the group of patients with CHD combined with HT and persistent AF as compared to the level of ET-1 (0.60 ± 0.06) fmol/l in the group of healthy people. The conducted correlation analysis showed a direct average relationship between the level of IL-1 β and ET-1 ($R = + 0.48$, with $p < 0.05$) and a strong direct relationship between the level of TNF- α and ET-1 ($R = + 0.79$, with $p < 0.05$) in the group of patients.

The follow-up period was 18 weeks, recurrences of AF have been reported in 25 patients, and 6 patients withdrew from the study. To study the effect of each factor on the probability of recurrence of AF the method of univariate logistic regression model was used. At that only the indicators that reliably demonstrated the prognostic value, were further studied using a multivariate analysis. The results of the logistic regression analysis are shown in Table 2.

Table 2. Prognostic value of the most significant variants for the recurrence of arrhythmias in patients with CHD combined with HT and persistent AF.

Variable	Univariate model		Multivariable model	
	χ^2 Wald's	P-value	χ^2 Wald's	P-value
Interleukin-1 β , PG/ml	8.86	0.004	-	-
FNO- α , PG/ml	15.43	0.0002	5.93	0.02
ET-1, fmol/l	10.65	0.002	5.89	0.02
Age, years	6.21	0.01	-	-
BMI, kg/m ²	6.83	0.01	-	-
Duration HT, years	0.71	0.40	-	-
Duration CHD, years	0.12	0.73	-	-
Duration PAF, years	1.59	0.21	-	-

As can be seen from Table. 2, independent predictors of recurrence of atrial fibrillation according to the results of multivariate analysis were TNF- α and Endothelin-1. The evaluation of the severity of endothelial dysfunction according to the concentration of Endothelin-1 and determination of the level of pro-inflammatory cytokines may have a prognostic value in relation to recurrence of arrhythmia in patients with CHD combined with HT and persistent AF.

The results obtained by us support the hypothesis that the level of cytokines is significantly higher in patients with AF in comparison with the control group [5]. The idea that inflammatory processes are involved in the pathogenesis of AF is not a new one, but the indications of an inflammatory state as a component of AF disease and its relation to several outcomes as recurrence of atrial fibrillation makes the study of inflammatory activity an interesting target for further investigation in this condition. Still it seems too early to include an unspecific indicator of inflammatory activity as a routine marker in the risk stratification of patients with AF [4].

Acknowledgements. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethical Declaration. The study was approved by the local ethics committee of State Institute «Zaporizhzhia Medical Academy of Postgraduate Education of Ministry of Health of Ukraine». The study was carried out in conformity with the Declaration of Helsinki.

References

- [1] 2012 focused update of the ESC Guidelines for the management of arterial fibrillation; An update of the 2012 ESC Guidelines for the management of atrial fibrillation; Developed with the special contribution of the European Heart Rhythm Association / A.J. Camm, G.Y. Lip, R. De Caterina [et al.] // European Heart Journal. – 2012. - Vol. 33. – P. 2719-2747.
- [2] ACC/AHA/ESC 2010 guidelines for the management of patients with atrial fibrillation-executive summary / A.J. Camm, P. Kirchhof, Y.H. Gregory [et al.] // Eur. Heart J. - 2010. - Vol. 31. - P. 2369-2429.
- [3] Engelman, Mads DM, and Jesper Hastrup Svendsen. "Inflammation in the genesis and perpetuation of atrial fibrillation." *European heart journal* 26.20 (2005): 2083-2092.

[4] Hijazi, Ziad, et al. "Biomarkers in atrial fibrillation: a clinical review." *European heart journal* 34.20 (2013): 1475-1480.

[5] Sata, Naoyuki, et al. "C-reactive Protein and Atrial Fibrillation Is inflammation a consequence or a cause of atrial fibrillation?." *Japanese heart journal* 45.3 (2004): 441-445.

Received: August 22, 2014; Published: October 22, 2014