THE NEW ARMENIAN MEDICAL JOURNAL
Vol.7 (2013), No 3, p.4-8

IMPACT OF INFLAMMATORY MARKERS ON PATHOGENESIS AND CLINICAL OUTCOMES AT DIFFERENT TYPES OF ATRIAL FIBRILLATION

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Received 12/11/2012; accepted in final form 8/12/2013

ABSTRACT

Patients (n=141) with non-rheumatic atrial fibrillation were observed. The study group involved subjects with paroxysmal, persistent, and permanent types of atrial fibrillation. According to gender, there were 84 (59.2%) men and 57 (40.8%) women. The age of patients ranged from 37 to 70 years (mean: 59.7±6.5 years). On average atrial fibrillation duration made 14.4±12.7 months. Among the examined patients, 129 (92.4%) subjects had ischemic heart disease, arterial hypertension was observed in 78 (56.1%) patients. Heart failure (NYHA functional class I-II) was detected in 104 (76.4%) patients; in 33 (23.6%) patients heart failure of NYHA functional class III was recorded. As a control group, 18 patients with ischemic heart disease and arterial hypertension without atrial fibrillation, similar in gender and age, were examined.

The analysis of data obtained showed that upon comparison of C-reactive protein levels in patients with paroxysmal and persistent type atrial fibrillation and in patients of control group the specified values were significantly higher in patients with atrial fibrillation. The comparison of C-reactive protein levels in permanent type atrial fibrillation patients with those of paroxysmal and persistent fibrillations revealed that the latter had significantly higher C-reactive protein levels.

A similar pattern was also observed in comparing the concentrations of interleukin-6. In particular, there was a significant increase in interleukin-6 concentration in patients with paroxysmal atrial fibrillation compared with permanent atrial fibrillation, as well as the concentration of interleukin-6 in patients with persistent and permanent type atrial fibrillation. Moreover, it was found that concentrations of interleukin-6 in patients with paroxysmal and persistent atrial fibrillation were also significantly higher than in patients of control group.

The research results signify that in patients with paroxysmal and persistent types atrial fibrillation the significant increase in concentrations of C-reactive protein and interleukin-6 was revealed, as compared with the permanent type atrial fibrillation and the control group. Consequently, an assumption may be drawn that the increase in concentrations of inflammatory markers might serve as a predictor of atrial fibrillation incidence or recurrence.

Keywords: *atrial fibrillation, inflammatory markers, interleukin-6, C-reactive protein.*

INTRODUCTION

Atrial fibrillation is the most common type of tachyarrhythmia and composes nearly 30% of all arrhythmias [*Falk R., 2001; Cheruku K. et al., 2004; Dernellis J., Panaretou M., 2005; Cosgrave J. et al., 2006; Grigoryan S. et al., 2009*]. Despite the fact that atrial fibrillation is one of the most common and studied cardiac arrhythmias, this disease continues to be associated with numerous scientific and practical problems related to atrial fibrillation pathogenesis, prognosis, and treatment.

The acute or chronic hemodynamic, metabolic, and, the most interesting, inflammatory aspects are considered as the pathogenic mechanisms. To

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some extent, all of them are able to bring forth structural remodeling of the atria, through which atrial fibrillation develops and progresses. In line with modern concepts it is assumed that one of the leading roles in atrial fibrillation pathogenesis belongs to the activation of immunological/inflammatory systems [*Avelis R. et al., 2003; Kushakovski M., 2004; Acevedo M. et al., 2005; Grigoryan S., Hazarapetyan L., 2007; Adamyan K. et al., 2008; Hazarapetyan L. et al., 2009*].

Among the wide range of biological and immunological markers used in clinical practice for evaluation of inflammation a specific role pertains to C-reactive protein (CRP), which belongs to the acute phase proteins of inflammation. In general, the concentration of CRP is regarded as the most sensitive and specific laboratory marker of inflammation and tissue damage; furthermore, CRP is correlated with the synthesis of interleukin-6 (IL-6), which in its turn plays an important role in inflammation development. The possibility of arrhythmias development under the impact of inflammatory markers triggered many studies dedicated to the inflammatory theory of arrhythmogenesis [*Boss Ch., Lip G., 2005; Grigoryan S., Hazarapetyan L., 2007*]. The results of morphology study demonstrated a serious argument in favor of this version. The biopsy of individuals suffering from idiopathic atrial fibrillation showed the inflammatory infiltrates, necrosis of myocytes and fibrosis [*Grigoryan S. et al., 2009; Grigoryan S. et al., 2010 a; b*]. Thus, it might be assumed that inflammation plays a specified role in the pathogenesis of atrial fibrillation. Therefore, it is interesting to assess the impact of inflammation on the clinical outcomes and recurrence of atrial fibrillation different types.

Hence, the purpose of this investigation was to evaluate the role of inflammatory markers (CRP and IL-6) in pathogenesis and clinical outcomes of atrial fibrillation different types.

Material and Methods

We observed 141 patients with non-rheumatic atrial fibrillation. The study included patients with paroxysmal, persistent, and permanent types of atrial fibrillation. There were 84 (59.2%) males, 57 (40.8%) females. The age of patients ranged from 37 to 70 years (mean: 59.7±6.5 years). On average atrial fibrillation duration made 14.4±12.7 months. Among the examined patients, 129 (92.4%) were diagnosed with coronary artery disease (ischemic heart disease); arterial hypertension was observed in 78 (56.1%) patients. Heart failure (HF) of NYHA functional class I-II was detected in 104 (76.4%) patients, while the HF of NYHA functional class III was recorded in 33 (23.6%) patients.

The exclusion criteria were as follows: ventricular arrhythmia (more than 30 beats per hour by B. Lown) and ventricular tachycardia; acute coronary syndrome; any surgery interventions within the last 4 weeks; heart failure (NYHA functional class above III); bronchial asthma; diabetes mellitus; acute inflammatory diseases within the last 4 months; non-coronary heart diseases (cardiomyopathies, myocarditises); valvular heart disease; Wolff-Parkinson-White syndrome; sick sinus syndrome; atrioventricular block and implanted pacemaker; thyroid gland dysfunction.

The clinical examination of patients at admission included a study of complaints, medical history, physical, laboratory-and-instrumental examination. Atrial fibrillationter that, patients were randomized to 3 groups depending on atrial fibrillation clinical types: paroxysmal atrial fibrillation (49 patients), persistent atrial fibrillation (23 patients) and permanent atrial fibrillation (71 patients). As a control group, we examined 18 patients with coronary artery disease and arterial hypertension without atrial fibrillation; this group was similar in gender and age. Table 1 reflects some parameters of patients with atrial fibrillation.

The program of investigation included general clinical examination of patients and additional methods: hemogram, lipidogram, electrocardiogram, echocardiogram, and biochemical blood tests (determination of coagulation indices and fibrino-

TABLE 1.

Some studied parameters of patients with atrial fibrillation

Indices	Mean values
Age (years)	59.70±6.49
Duration of atrial fibrillation (months)	14.40 ±12.70
Left atrium size (*mm*)	42.289 ±3.68
End-diastolic size of left ventricle (*mm*)	56.69±3.84
Ejection fraction (%)	46.63±5.48
Left ventricle wall thickness (*mm*)	12.44±2.50

gen), as well as quantification of CRP and IL-6 levels. Cytokine levels in plasma were determined by EIA (ELISA) on "Stat Fax 303 Plus" analyzer ("Awareness", USA) using "Human IL-6" commercial kits ("BioSource", Belgium) for IL-6 and "hs-CRP" kits ("DRG International Inc.", USA) for CRP. The concentrations of CRP were measured in *mg/L*, those of IL-6 - in *pg/ml*. Treatment regimes of all patients included standard hospital therapy for atrial fibrillation treatment.

Studies were conducted on the basis of simple randomized open-label protocols using the universal statistical packages SPSS 13.0 and EXCEL-2007. For estimation of the intergroup differences we used the parametric Students *t*-test. Data were presented as M±m; statistically significant difference was considered at $p<0.05$.

RESULTS AND DISCUSSION

We carried out a comparative assessment of CRP and IL-6 concentrations in patients with atrial fibrillation different types (Table 2).

The analysis of data obtained showed that in patients with paroxysmal and persistent atrial fibrillation there were no significant differences between the revealed levels of both CRP and IL-6 (Table 2; Figures 1-2). As revealed, CRP and IL-6 levels in patients with permanent atrial fibrillation compared with the control group also did not differ significantly (Table 2; Figures 1-2). However, when comparing the levels of CRP in patients with paroxysmal and persistent atrial fibrillation types and those in control group patients, we found that CRP level was significantly higher in patients with atrial fibrillation (Table 2; Figure 1). Upon comparison of CRP levels in patients with permanent atrial fibrillation and paroxysmal and persistent type fibrillations we revealed that in the latter patient group there were observed CRP significantly high levels (Table 2; Figure 1). The similar pattern was also observed, when comparing IL-6 levels in paroxysmal and persistent atrial fibrillation patients with those in permanent fibrillation patients and the control group patients. In particular, there was a statistically significant increase in IL-6 concentration in patients with paroxysmal atrial fibrillation compared to patients with the permanent atrial fibrillation (Table 2; Figure 2), as well as compared to levels of IL-6 in patients with persistent and permanent atrial fibrillation. Moreover, it was found that IL-6 concentrations in patients with paroxysmal and persistent types atrial fibrillation were also significantly higher than in the control group of patients (Table 2; Figure 2).

Similar results were obtained by A. Hernández and co-authors (2006), who showed that under CRP concentration increase the risk of atrial fibrilation recurrence was elevated. Hence, the authors considered that CRP as inflammation acute-phase protein was most likely to react to the appearance of atrial fibrillation. The conclusion was drawn about CRP as the risk marker of atrial fibrillation incidence

TABLE 2.

The comparison of CRP and IL-6 mean values in patients with atrial fibrillation different types

Indices	Paroxysmal n=49	Persistent n=23	Permanent n=71	Control group n=18
C-reactive protein, *mg/L*	**5.7 ± 1.1**	**4.8 ± 0.5** $0.25>p_1>0.1$	**3.2 ± 0.7** $0.05>p_1>0.025$ $0.05>p_2>0.025$	**3.1 ± 0.6** $0.005>p_1>0.0005$ $0.025>p_2>0.01$ $p_3>0.4$
interleukin-6, *pg/ml*	**35.3 ± 5.1**	**33.5 ± 5.7** $p_1>0.4$	**20.4 ± 3.5** $0.05>p_1>0.025$ $0.05>p_2>0.025$	**19.7 ± 5.0** $0.025>p_1>0.01$ $0.05>p_2>0.025$ $p_3>0.4$

Notes: p_1 – data of persistent, permanent atrial fibrillation and control group related to the paroxysmal type;
p_2 – data of permanent atrial fibrillation and the control group related to the persistent type;
p_3 – data of control group related to the permanent type atrial fibrillation.

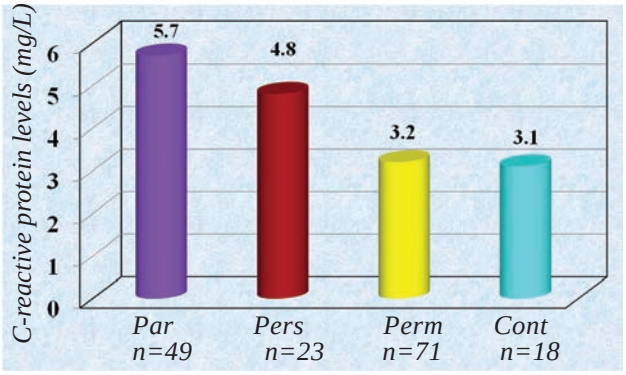

FIGURE 1. *Comparative assessment of C-reactive protein mean values in patients with atrial fibrillation different types.* ***NOTES:*** *par. – paroxysmal, pers. – persistent, perm – permanent type atrial fibrillations.*

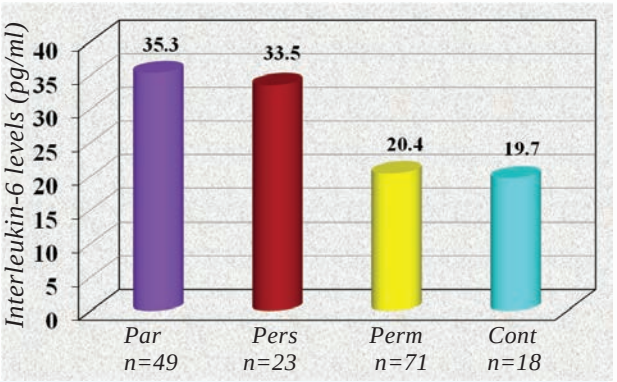

FIGURE 2. *Comparative assessment of interleukin-6 concentrations in patients with atrial fibrillation different types.* ***NOTES:*** *par. – paroxysmal, pers. – persistent, perm – permanent type atrial fibrillations.*

[*Hernandez A., 2006; Loricchio M. et al., 2007; Guidelines, 2010*]. A similar opinion was also held by some other researchers, who showed that low levels of CRP and IL-6 were associated with successful cardioversion and low risk of atrial fibrillation recurrence [*Boss Ch., Lip G., 2005; Dernellis J., Panaretou M., 2005*]. At the same time, the opposite opinion is discussed in scientific literature. In contrast to many other authors, J. Cosgrave and coworkers, showed that CRP concentration was not associated with successful or unsuccessful cardioversion [*Cosgrave J. et al., 2006*].

CONCLUSION

However, despite some contradictory positions on the role of inflammation in atrial fibrillation, our findings indicated that in patients with paroxysmal and persistent types of atrial fibrillation a statistically significant increase in CRP and IL-6 levels was revealed as compared with the permanent type of atrial fibrillation and the control group patients.

Consequently, we can assume that the increase in concentrations of inflammatory markers may present as a predictor of paroxysmal atrial fibrillation or even its recurrence.

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