MERIT RESEARCH JOURNALS
www.meritresearchjournals.org

Merit Research Journal of Medicine and Medical Sciences (ISSN: 2354-323X) Vol. 3(7) pp. 271-277, July, 2015
Available online http://www.meritresearchjournals.org/mms/index.htm

Original Research Article

Interleukin-4 and Paroxysmal Atrial Fibrillation

Mariya Negreva[1*], Svetoslav Georgiev[2], Krasimira Prodanova[3], Katerina Vitlianova[4] and Daniela Arabadzhieva[5]

[1]*First Clinic of Cardiology, Varna University Hospital "St. Marina", 1 H. Smirnenski blvd, 9010 Varna, Bulgaria

[2]Second Clinic of Cardiology, Varna University Hospital "St. Marina", 1 H. Smirnenskiblvd, 9010 Varna, Bulgaria

[3]Faculty of Applied Mathematics and Informatics, Technical University of Sofia, Bulgaria

[4]Clinic of Cardiology, Second City Hospital, 120 Hr. Botevstr, 1202 Sofia, Bulgaria

[5]First Clinic of Neurology, Varna University Hospital "St. Marina", 1 H. Smirnenskiblvd, 9010 Varna, Bulgaria

***Corresponding Author's E-mail: mnegreva@abv.bg**
Tel: +359 888 487 303
Fax: +359 52 302 881

Abstract

The purpose of this study was to study the IL-4 plasma concentrations in patients with paroxysmal atrial fibrillation (PAF) (< 48 hours). The marker was investigated in 51 patients (26 males, 25 females; mean age 59.84±1.60 years) at their hospital admission as well as twenty-four hours and twenty-eight days after sinus rhythm restoration. Fifty-two controls (26 males, 26 females; 59.50±1.46 years) were selected. Sinus rhythm was restored by means of propafenone. The IL-4 concentrations were measured using an ELISA kit. The mean duration of AF episodes till the hospitalization was 8.14 hours. On admission, the IL-4 concentrations were elevated as compared to those of the controls (54.26±1.89 vs 35.20±1.55 pg/mL, p<0.001). Twenty-four hours after rhythm regularization, the changes persisted (48.62±1.17 vs 35.20±1.55 pg/mL, p<0.001). On the twenty-eighth day, no significant difference was observed (37.90±2.05 vs 35.20±1.55 pg/mL, p=0.2). The logistic regression analysis indicated that IL-4 was a statistically significant predictor for PAF. The specific dynamics of IL-4 levels is indicative of a marked inflammatory and fibrosis activity still in the early hours of PAF, whose consequences cumulate even after rhythm regulation. IL-4 has a predictive value for PAF that may help in the management of the disease.

Keywords: Atrial fibrillation, Fibrosis, Inflammation, Interleukin 4, Prediction

List of abbreviations
PAF – Paroxysmal Atrial Fibrillation
AF – Atrial Fibrillation

INTRODUCTION

Atrial fibrillation (AF) is the commonest rhythm disorder in clinical practice affecting >1% of the total population (Potpara et al., 2011). The medication and non-medication methods of treatment established so far, have proved to have unsatisfactory efficiency (Sovari et al., 2010). It is considered that their major drawback is the lack of a purposeful impact on of the mechanisms associated with the initiation, persistence and recurrences of AF (Mayyas et al., 2013). Therefore, for the last years, namely the pathophysiological processes determining the manifestation and clinical course of the disease have been in the focus of a particular clinical and research interest.

An increasing attention has been paid to the inflammatory process and its role in AF. Studies have shown elevated levels of a number of systemic biomarkers such as IL-6, TNF-α, CRP etc., and the values of some of them prove even to be predictive about the development of the rhythm disorder (Aviles et al., 2003; Psychari et al., 2005; Sata et al., 2004; Celebi et al., 2011). The anti-arrhythmic effect of corticosteroids and statins in some clinical and experimental investigations have also indirectly proved the involvement of inflammation in the AF manifestation (Reilly et al.,

2011; Dernellis et al., 2004; Halonen et al., 2007).

Meanwhile, the results of the histological investigations confirm that the development of AF is associated with structural changes in the atrial myocardium, i.e. “structural remodeling of the atria” whose main morphological substrate is the interstitial fibrosis (Wakili et al., 2011; Nattel et al., 2008; Nattel, 2002). It alters the electrophysiological properties of the myocardium and creates conditions for the emergence of abnormal automaticity, triggered activity or re-entrant wavelets in the atria. This electrical heterogeneity predisposes to AF and subsequently facilitates the recurrences and the maintenance of the rhythm disorder.

To the moment, the link between the established fibrosis and inflammatory processes in AF has not been sufficiently clarified. Neither have the molecular mechanisms responsible for the fibrosis of the atrial myocardium been entirely clarified.

Interleukin 4 (IL-4) is the main anti-inflammatory interleukin with prominent pro-fibrosis properties. In this respect, it may be appropriate to investigate it and find out about its importance for the clinical course of AF, which motivated us to conduct our study.

Purpose

To study the changes of IL-4 in patients with paroxysmal atrial fibrillation (PAF) (< 48 hours) by determining its plasma concentrations three times, namely during the rhythm disorder, twenty-four hours and twenty-eight days after sinus rhythm restoration.

MATERIAL AND METHODS

Study population

Subject to the study were patients with PAF with a history of the rhythm disorder < 48 hours, which allowed for an acute medication attempt to restore sinus rhythm. The duration of the PAF episode was established by means of a detailed history taking. The patients determined the onset of the arrhythmia as a sudden appearance of “palpitations”, continuing still at the moment of hospitalization. The diagnosis “atrial fibrillation” was accepted after its confirmation by the electrocardiographic investigation made immediately after the patients’ hospitalization.

A total of 338 patients were screened from those hospitalized at the Intensive Cardiology Unit at University Hospital “St. Marina” – Varna, Bulgaria, for the period 10.2010 – 05.2012. Due to exclusion criteria (see below), only 79 patients remained in the study. Propafenone was applied to all of them for sinus rhythm restoration. An unsuccessful regularization or a recurrence of AF gave us reasons to exclude another 23 patients till the end of the study.

In the remaining 56 participants (31 male, 25 female), sinus rhythm was restored and was permanently retained till the end of the study.

The patients were followed for 28 days after arrhythmia discontinuation. Two control check-ups were performed – on the seventh and twenty-eighth day following the sinus rhythm restoration. The ECG recordings together with the detailed history taking did not indicate a recurrence of the sinus rhythm disorder. Subsequently, to equalize the gender structure of the patient group, 51 patients (26 male 25 female) were consistently selected with mean age 59.84±1.60 years (31-77 years).

For the formation of the control group, the exclusion criteria valid for the patients’ group were applied (see below). The selection of the participants in the study (patients and controls) aimed at eliminating to a maximum degree or equalizing the factors which could exert influence on the plasma concentrations of IL-4 between the two groups. Out of a total of 169 screened, 52 were selected as controls for the study. Their mean age was 59.50±1.46 years (30-76 years), male and female being of equal number 26 (50%).To the moment of the study the controls did not have history or electrocardographic data for AF.

The study was undertaken after the approval of the Scientific Research Ethics Commission (№35/29.10.2010) at University hospital “St. Marina” – Varna, Bulgaria and in accordance with the ethical norms of the Helsinki Declaration for experimentations in human subjects (WMA Declaration of Helsinki, 2008).

All participants (patients and controls) were included in the study following preliminary signing of informed consent.

Exclusion criteria for the study

1. Cardiovascular diseases, namely: ischemic heart disease, heart failure; uncontrollable hypertension; 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; neoplasmic or autoimmune diseases; diseases of the endocrine nervous system (except for diabetes mellitus type 2, non-insulin dependent, well controlled).
3. Intake of hormone-replacement therapy or contraceptives; pregnancy; systematic intake of analgesics, incl. non-steroidal anti-inflammatory drugs.

Therapeutic scheme for propafenone

Propafenone was applied according to the established

Table 1. Characteristics of patients' and control group.

	Patients with PAF	Control group	P values
Number of participants in the group	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

scheme, e.g. i.v. 2 mg/kg bolus, followed by infusion in a dose of 0.0078 mg/kg/min for 120 min. and p.o. intake in a dose of 300 mg three times at an interval of 8 hours (Bellandi et al., 1995; Bianconi et al., 1998). In case of sinus rhythm restoration, the scheme was discontinued and till the end of the study the patients were given a maintaining dose of propafenone p.o. 150 mg three times daily. All the patients were constantly monitored until their dehospitalisation, e.g. 24 hours after the sinus rhythm restoration.

Collection and storage of blood samples. Investigation of IL-4

The patients' venous blood was collected three times: immediately after their hospitalization in the ward, twenty-four hours and twenty-eight days after sinus rhythm restoration. The controls were investigated once.

The blood samples were withdrawn in a heparin vacutainer (VACUETTE/4.0 ml/Li Hep) and were immediately centrifuged for 15 minutes at 1000xg at 4ºC within 30 minutes of collection. The obtained plasma was separated from the erythrocytes and immediately frozen and stored in accordance with the methodology.

All the samples were coded after their collection which did not allow for their identification during the laboratory investigations.

During the study, no repeated freezing of the samples was permitted. Plasma concentrations of IL-4 were measured using an enzyme-linked immunosorbentassay (ELISA, Elabscience Biotechnology Co., Ltd, China) according to the manufacturer's protocol.

Statistical analysis

Descriptive analysis was used for the calculation of mean values, relative shares and the central trend (Mo=mode). The testing for hypotheses for equality of mean values and indicators of relative shares was performed by means of Student's t-criterion. Values $p<0.05$ were adopted for statistically significant. To identify IL-4 statistically significant (prognostic) factor for the occurrence of PAF, the logistic regression model was used.

The analysis of all data was performed by means of special packet for statistical analyses GraphPad PRISM, Version 5.00. All the results were presented as a mean value±standard error of the mean arithmetic (SEM) or n(%).

RESULTS

Clinical characteristics of patients' and control group

According to the indicators: number, mean age and gender structure, the patients' group was comparable to the control one ($p>0.05$) (Table 1). Concerning accompanying diseases, dyslipidemia and administered treatment (till the moment of hospitalisation) as well as the incidence of deleterious habits and BMI, the groups did not have statistically significant differences ($p>0.05$) (Tables 2 and 3).

The data from the transthoracic echocardiographic investigation confirmed the absence of structural heart diseases in the patients and the controls and at the same time they did not show statistically significant differences in the investigated indicators ($p>0.05$) (Table 4).

The study considered that the formation of the control group, which is identical to the patients' group in terms of the indicators mentioned above (Tables 1-4), makes the comparison between the groups objective to a maximum degree and eliminates their impact on the investigated indicator.

The statistical analysis of the history of AF till the moment of hospitalization indicated that all patients were hospitalized between the second and the twenty-fourth hour after the onset of the arrhythmia, and most frequently on the fifth hour (Mo=5; 10 out of all 51 patients). The mean duration of AF till the moment of hospitalization was 8.14±0.76 hours.

Plasma concentration of IL-4

Figure 1 shows that upon admission to the hospital ward, the patients' plasma levels of IL-4 (baseline values) were elevated in comparison to those of the controls (54.26±1.89 vs 35.20±1.55 pg/mL, $p<0.001$). Twenty-four hours following the sinus rhythm restoration, the measured values of IL-4 remained significantly higher as compared to the controls (48.62±1.17 vs 35.20±1.55 pg/mL, $p<0.001$). On the twenty-eighth day after the rhythm regularization no significant difference was

Table 2. Accompanying diseases, dyslipidemia and their treatment.

	Patients with PAF number (%)	Control group number (%)	P values
Accompanying diseases			
Hypertension	37 (72.54%)	34 (65.38%)	p=0.44
Diabetes mellitus type 2	3 (5.88%)	2 (3.84%)	p=0.62
Chronic ulcer disease	2 (3.92%)	0	p=0.15
Status after hysterectomy	2 (3.92%)	1 (1.92%)	p=0.54
Benign prostatic hyperthrophy	1 (1.96%)	0	p=0.32
Dyslipidemia	4 (7.84%)	3 (5.77%)	p=0.69
Medicaments 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

Table 3. Deleterious habits and BMI in patients and controls.

	Patients with PAF Number (%)	Control Group Number (%)	P values
Deleterious 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

Table 4. Results from transthoracic echocardiography.

	Patients with PAF	Control group	P values
Echocardiographic measurements			
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 (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

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

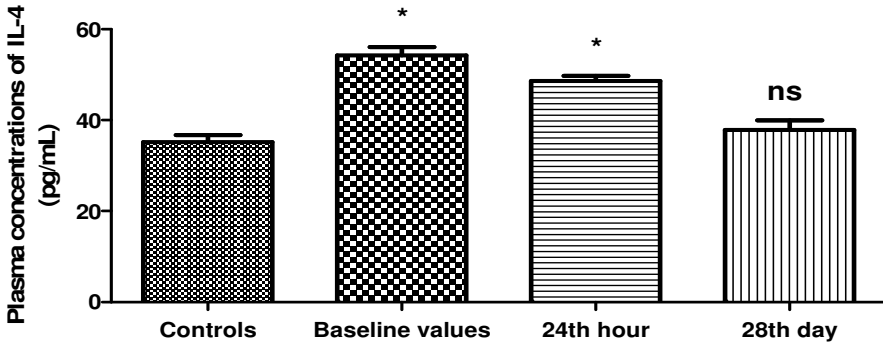

Figure 1. Changes in plasma concentration of IL-4 (pg/mL) in patients with PAF. (baseline values – IL4 values upon patients' hospitalization; 24th hour – values 24 hours after sinus rhythm restoration; 28th day - values 28 days after sinus rhythm restoration; *- p<0.001; ns – statistically insignificant difference).

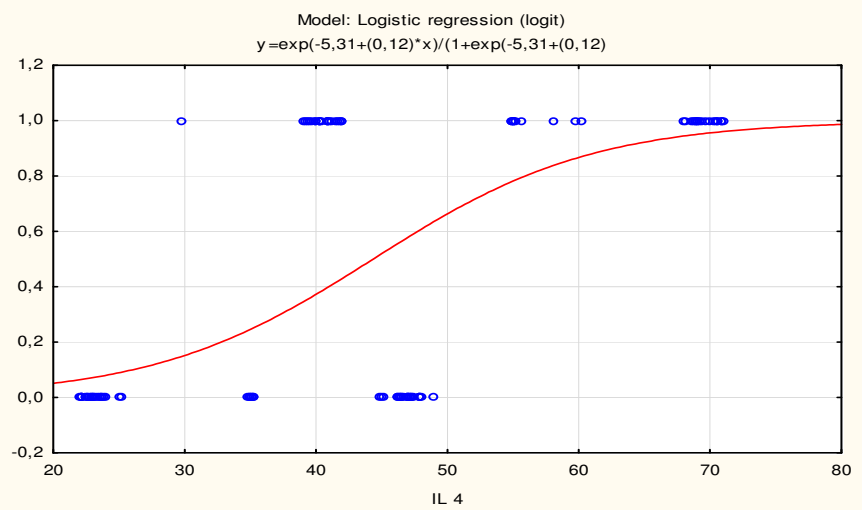

Figure 2. Probability distribution of IL-4 estimated using logistic model.

established between the values of the patients and the controls (37.90±2.05 vs 35.20±1.55 pg/mL, p=0.2).

The logistic regression model with a single explanatory variable showed that IL-4 was a statistically significant predictor for PAF manifestation (p<0.001). The fitted equation indicated that as the IL-4 concentrations increased, the probability for presence of PAF also increased ($\hat{\beta}_1 = 0,12 > 0$) (Figure 2).

DISCUSSION

IL-4 is a 15-kd monomer (129 amino acids) produced mainly by Th2-cells and to minor extent by basophils, eosinophils and mast cells. It was discovered in 1982 and was initially described as a B-cell growth factor I (BCGF-I) (Howard et al., 1982). Nowadays, it is known that it possesses pleiotropic properties. IL-4 regulates the allergic reactions as well as the protective immune response against helminthes and other extracellular parasites, suppresses Th1-cell development and induces IgE class switching. In addition, it is one of the main modulators of inflammation. In its nature, it is an anti-inflammatory cytokine fulfilling its functions mainly by suppressing the pro-inflammatory environment. IL-4 inhibits the production of the major for the inflammatory cascade pro-inflammatory cytokines IL-1, IL-6 and TNF-α while stimulating production of the major anti-inflammatory cytokines IL-1ra and IL-10 (Akdis et al., 2011; Steinke et al., 2006).

The result of the study showed significant changes in the plasma concentrations of IL-4 in patients with PAF. The measured baseline values of the indicator were increased as compared to the controls (p<0.001), which may be accepted for an indirect sign of enhanced production of the pro-inflammatory cytokines IL-1, IL-6 and TNF-α at this stage of the disease. It is a well-known fact that the inflammatory response is determined by complex interactions between the pro- and anti-inflammatory mediators. The appropriate balance between them is a prerequisite for the restoration of the homeostasis. Its disturbance due to enhanced release of pro-inflammatory cytokines leads to excessive inflammatory response (Marie et al., 1996). In view of the facts above, our results give us grounds to admit that the clinical manifestation of PAF is associated with enhanced inflammatory processes caused by increased production of IL-1, IL-6 and TNF-α. In the meantime, an adaptive response by the anti-inflammatory cytokine IL-4 is also present.

Changes in the interleukin cascade in AF have been reported in other studies. Thus, for example, Conway et al. (2004) and Marcus et al. (2010) independently measure elevated levels of IL-6 in chronic AF, and Psychary et al. (2005) even prove their direct correlation to the history of the rhythm disorder and the left atrium diameter. Wu et al. study postoperative AF patients undergoing coronary artery bypass surgery who are characterized by elevated levels of IL-8, and according to Hak et al., in this group of patients IL-2 has a predictive value for the manifestation of postoperative AF (Wu et al., 2008; Hak et al., 2005). Data are extremely scarce about the interleukin status of patients with PAF. Thus, for example, Sata et al. (2004) measure increased levels of IL-6 and TNF-α, which persist to be elevated for two weeks after rhythm regularization. No studies are available on the levels of IL-4.

It has to be emphasized that our study does not only investigate for the first time the plasma concentrations of IL-4 in PAF but also changes in the indicator are measured in the early hours of the clinical manifestation of the rhythm disorder, e.g. up to the 24th hour after its onset (average 8.14 hours). It is exactly this fact that

gives serious grounds to assume that our results are not just an occasional laboratory finding but are directly related to the clinical manifestation of the disease. They are likely to be a part of the complex and so far insufficiently clarified intimate mechanisms of the disease.

The logistic regression analysis showed that IL-4 is a laboratory indicator of the inflammation whose values are predictive about the development of PAF. The probability for the patient to manifest AF grows with the increase of the IL-4 values.

As mentioned above, IL-4 is a pleiotropic cytokine, which apart from the immune inflammatory response, takes part in the process of tissue fibrosis. It activates the synthesis of collagen I and collagen III and thus contributes to the progress of fibrosis (Roselló-Lletí et al., 2007). IL-4 possesses a marked pro-fibrosis action which in itself could have an utmost importance for the development of AF. It is known that the structural changes in the atria are of key importance for the manifestation, recurrences and chronification of AF. It is considered that, unlike in electrophysiological remodeling, structural remodeling begins to develop several weeks after the AF onset (Korantzopoulos e al., 2003). Our results, however, indicate the presence of pro-fibrosis activity still in the early hours of the clinical manifestations of the disease. This suggests the accumulation of fibrosis changes in the atrial myocardium still in the early episodes of the arrhythmia. The question inevitably arises about the interrelation between the initial episodes of AF, their anti-recurrence treatment and the long-term prognosis of the disease.

For the first time, atrial remodeling is associated with the inflammatory process by Frustaci et al. in 1995. In histological samples from patients with isolated AF, they detect pronounced inflammatory infiltrates together with myocardial necrosis and fibrosis (Frustaci et al., 1997). In experimental animal models of AF, Nakamura et al. confirm the presence of atrial perimyocarditis with inflammatory infiltrates, lipid degeneration and fibrosis (Nakamura et al., 2003). The molecular mechanisms associated with these changes remain not entirely clear to date. IL-4 with its pleiotropicproperties is a possible mediator between structural remodeling and inflammation.

The results obtained 24 hours after the discontinuation of the rhythm disorder presents no lesser clinical interest. IL-4 retained its elevated values ($p<0.001$). It turns out that an inflammatory process is present not only during the clinical manifestations of the arrhythmia but also after it.

Twenty-eight days after the discontinuation of the rhythm disorder, the plasma concentrations of IL-4 are markedly decreased and do not differ from the controls ($p=0.2$). Although time-consuming, the recovery of the sinus rhythm is associated with reduction of the inflammatory processes.

CONCLUSION

The clinical manifestation of PAF is associated with elevated concentrations of IL-4, persisting after the arrhythmia episode and restoring gradually with time. The specific dynamics of IL-4 levels is indicative of a marked inflammatory and fibrosis activity still in the early hours of PAF, whose consequences cumulate even after the rhythm regulation. IL-4 has a predictive value for PAF, which may prove it a valuable laboratory marker when determining the therapeutic approach to patients with PAF.

Conflicts of Interest

The authors have no conflicts to declare concerning this article.

REFERENCES

Akdis M, Burgler S, Crameri R, Eiwegger T, Fujita H, Gomez E, Klunker S, Meyer N, O'Mahony L, Palomares O, Rhyner C, Ouaked N, Schaffartzik A, Van De Veen W, Zeller S, Zimmermann M, Akdis CA (2011). Interleukins, from 1 to 37, and interferon-γ: receptors, functions, and roles in diseases. J Allergy ClinImmunol. 127(3):701-21.

Aviles RJ, Martin DO, Apperson-Hansen C, Houghtaling PL, Rautaharju P, KronmalRA, Tracy RP, Van Wagoner DR, Psaty BM, Lauer MS, Chung MK (2003). Inflammation as a risk factor for atrial fibrillation. Circulation. 108:3006-3010.

Bellandi F, Cantini F, Pedone T, Palchetti R, Bamoshmoosh M, Dabizzi RP (1995). Effectiveness of Intravenous Propafenone for Conversion of Recent-Onset Atrial Fibrillation: A Placebo-Controlled Study. Clin. Cardiol. 18: 631-634.

Bianconi L, Mennuni M (1998). Comparison Between Propafenone and Digoxin Administered Intravenously to Patients With Acute Atrial Fibrillation. Am J Cardiol. 82:584-588.

Celebi OO, Celebi S, Canbay A, Ergun G, Aydogdu S, Diker E (2011). The effect of sinus rhythm restoration on high-sensitivity C-reactive protein levels and their association with long-term atrial fibrillation recurrence after electrical cardioversion. Cardiology. 118:168-174.

Conway DS, Buggins P, Hughes E, Lip GY (2004). Relationship of interleukin-6and C-reactive protein to the prothrombotic state in chronic atrialfibrillation. J Am CollCardiol. 43:2075-82.

Dernellis J, Panaretou M (2004). Relationship between C-reactive protein concentrations during glucocorticoid therapy and recurrent atrial fibrillation. Eur Heart J. 25(13):1100-7.

Frustaci A, Chimenti C, Bellocci F, Morgante E, Russo MA, Maseri A (1997). Histological substrate of atrial biopsies in patients with lone atrial fibrillation. Circulation. 96:1180–1184.

Hak Ł, Myśliwska J, Wieckiewicz J, Szyndler K, Siebert J, Rogowski J (2009).Interleukin-2 as a predictor of early postoperative atrial fibrillation after cardiopulmonary bypass graft (CABG).J Interferon Cytokine Res. 29(6):327-32.

Halonen J, Halonen P, Järvinen O, Taskinen P, Auvinen T, Tarkka M, Hippeläinen M, Juvonen T, Hartikainen J, Hakala T (2007).Corticosteroids for the prevention of atrial fibrillation after cardiac surgery: a randomized controlled trial. JAMA. 297(14):1562-7.

Howard M, Farrar J, Hilfiker M, Johnson B, Takatsu K, Hamaoka T, Paul WE (1982). Identificationof a T cell-derived b cell growth factor distinct from interleukin 2.J Exp Med. 155:914-23.

Korantzopoulos P, Kolettis T, Siogas K, Goudevenos J (2003).Atrial fibrillation and electrical remodeling: the potential role of inflammation and oxidative stress. Med SciMonit. 9(9):RA225-9.

Marcus GM, Smith LM, Ordovas K, Scheinman MM, Kim AM, Badhwar N, Lee RJ, Tseng ZH, Lee BK, Olgin JE (2010). Intracardiac and extra cardiac markers of inflammation during atrial fibrillation. Heart Rhythm. 7(2):149-54.

Marie C, Pitton C, Fitting C, Cavaillon JM (1996).Regulation by anti-inflammatory cytokines (IL-4, IL-10, IL-13, TGFbeta) of interleukin-8 production by LPS- and/ or TNFalpha-activated human polymorphonuclear cells. Mediators Inflamm. 5(5):334-40.

Mayyas F, Alzoubi KH, Van Wagoner DR (2013). Impact of aldosterone antagonists on the substrate for atrial fibrillation: aldosterone promotes oxidative stress and atrial structural/electrical remodeling. Int J Cardiol. 168(6):5135-42.

Nakamura Y, Nakamura K, Fukushima-Kusano K, Ohta K, Matsubara H,Hamuro T, Yutani C, Ohe T (2003). Tissue factor expression in atrial endothelia associated with nonvalvular atrial fibrillation: possible involvement in intracardiac thrombogenesis. Thromb Res 111:137–142.

Nattel S (2002).New ideas about atrial fibrillation 50 years on. Nature. 415(6868):219-26.

Nattel S, Burstein B, Dobrev D (2008). Atrial remodeling and atrial fibrillation: mechanisms and implications. Circ Arrhythm Electrophysiol. 1(1):62-73.

Potpara TS, Lip GY (2011). Lone atrial fibrillation: what is known and what is to come. Int J ClinPract. 65(4):446-57.

Psychari SN, Apostolou TS, Sinos L, Hamodraka E, Liakos G, Kremastinos DT (2005). Relation of elevated C-reactive protein and interleukin-6 levels to left atrial size and duration of episodes in patients with atrial fibrillation. Am J Cardiol. 95:764-767.

Reilly SN, Jayaram R, Nahar K, Antoniades C, Verheule S, Channon KM, Alp NJ, Schotten U, Casadei B (2011).Atrial sources of reactive oxygen species vary with the duration and substrate of atrial fibrillation: implications for the antiar rhythmic effect of statins. Circulation. 124(10):1107-17.

Roselló-Lletí E, Rivera M, Bertomeu V, Cortés R, Jordán A, González-Molina A (2007).Interleukin-4 and cardiac fibrosis in patients with heart failure. Rev EspCardiol. 60(7):777-80.

Sata N, Hamada N, Horinouchi T, Amitani S, Yamashita T, Moriyama Y, MiyaharaK (2004). C-reactive protein and atrial fibrillation. Is inflammation a consequence or a cause of atrial fibrillation? Jpn Heart J. 45:441–445.

Sovari AA, Dudley SC (2010). Atrial fibrillation and oxidative stress. In: Sauer H, Ajay MS, Laurindo FR, editors. Studies in Cardiovascular Disorders. 1. Humana Press; pp. 373–89.

Steinke JW, Negri J, Enelow R, Baramki DF, Borish L (2006). Proinflammatory effectsof IL-4 antagonism. J Allergy ClinImmunol. 118:756-8.

Wakili R, Voigt N, Kääb S, Dobrev D, Nattel S (2011).Recent advances in the molecular pathophysiology of atrial fibrillation.J Clin Invest. 121(8):2955-68.

World Medical Association Declaration of Helsinki (2008). Ethical principles for medical research involving human subjects. 59th WMA General Assembly. Seoul.

Wu ZK, Laurikka J, Vikman S, Nieminen R, Moilanen E, Tarkka MR (2008).High postoperative interleukin-8 levels related to atrial fibrillation in patients undergoing coronary artery bypass surgery. World J Surg. 32(12):2643-9.