Increased IL-17A in Atrial Fibrillation Correlates with Neutrophil to Lymphocyte Ratio

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ABSTRACT

Background: Atrial Fibrillation (AF) is the most common cardiac arrhythmia and an independent risk factor for stroke among the elderly. A role for inflammation in the atrial remodeling as well as development and recurrence of AF is known. **Objective:** To compare IL-17A between patients with different types of AF and healthy individuals. **Methods:** IL-17A was measured in sera of 112 patients and 107 healthy age/sex-matched controls using ELISA assay. In sera of 26 patients with elevated IL-17A (>1 Pg/ml), CCL5 and CCL18 levels were also measured. **Results:** IL-17A was significantly increased in patients with AF compared to controls (1.28 ± 3.5 vs. 0.19 ± 0.64 Pg/ml, p=0.001). There was no significant difference in the level of IL-17A between different types of AF. IL-17A was significantly higher in patients with a history of coronary artery bypass graft compared to other patients (p=0.01). A significant positive correlation between IL-17A and CCL18 concentration was found (p=0.001). An increase in the Neutrophil/Lymphocyte ratio (NLR) was observed in patients with elevated serum IL-17A compared to other patients (p=0.006). Male patients showed higher increase in NLR (p=0.007) which was accompanied by a decrease in CCL5 (p=0.000) and a marginal increase in CCL18 (p=0.085) compared to females. There was an increase in CCL5 levels in patients receiving Acetylsalicylic Acid (ASA) therapy (p=0.046). **Conclusions:** The increase in IL-17A levels is related to the AF pathology mediated by neutrophils and monocytes. The current study signifies the role of immune cells and cytokines in the pathology of AF.

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Keywords: Atrial Fibrillation, CABG, CCL5, CCL18, IL-17A, Neutrophil

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INTRODUCTION

Inflammation is a long known pathogenic phenomenon in many diseases; however, many aspects of this phenomenon are yet to be understood. In addition to the traditionally known IL-6, TNF-α, IL-1, and C-reactive protein (CRP), the discovery of the IL-17 family of cytokines has added more complexity to the mediators and cellular players in inflammatory conditions. Interleukin-17A (IL-17A), an immune inflammatory cytokine, is one of the key mediators of the activation, recruitment, and migration of neutrophils after a specific immune response is shaped (1). Interestingly, IL-17A treatment of mice macrophages results in the production of CCL5, CCL4, and several other cytokines which may play a role in the recruitment of neutrophils and inflammatory leukocytes to the inflamed tissue (2). This observation suggests that IL-17A, being a part of T cell response, can trigger the effector function of macrophages in inflammatory reactions. Th17 cells are the main producers of IL-17A and the lineage commitment of naive T cells to Th17 cells is shown to be dependent on IL-6 (3). IL-17A has been implicated not only in the defense against cancer and infection, but also in the pathology associated with inflammatory responses (4). The elevation of IL-17A in the sera of patients with Ischemic Heart Disease (IHD), including acute myocardial infarction and unstable angina, is already reported (5). Moreover, the effect of sleep deprivation on increased heart rate and serum CRP and thereby increased risk of cardiovascular diseases may be exerted through elevated lymphocyte activation and the production of IL-1β, IL-6 and IL-17A (6). As the most common cardiac arrhythmia among the elderly, Atrial Fibrillation (AF) is accompanied by irregular and rapid atrial activation which results in a decreased cardiac output (7). Inflammation has been documented as an important factor in the genesis and continuation of AF (8). The elevated atrial leukocyte infiltration reported in lone and structural AF is suggested to predict post-surgery AF (9-12). Infiltrating mononuclear cells and activated leukocyte subsets are amongst the main players in matrix metalloproteinase (MMP) activation and deposition of collagen and fibrin in the atrium (13). Moreover, atrial fibrosis has been considered as one of the key events in transition from paroxysmal to persistent or permanent AF (14). Interestingly, fibroblasts, cardiac epithelial and endothelial cells as well as circulating cells can differentiate to activated cytokine producing myofibroblasts under mechanical and chemical stress as well as cytokines and growth factors (15,16). In addition to MMP-8, MMP-9 and MPO, inflammatory proteins and cytokines such as CRP and IL-6, produced by leukocytes, are associated with the development and recurrence of AF, along with successful cardioversion (17-19). In a mouse model of experimental autoimmune myocarditis (EAM), increased IL-17 serum levels, increased lymphocyte infiltration, collagen deposition, and fibrosis in myocardium occurred proceeding from day 21 to day 54 (20). The authors beautifully showed that IL-17 triggered cardiac fibrosis by affecting PKC-β and Erk 1/2 phosphorylation and NF-κB activation in fibroblasts, which expressed IL-17 receptor A (IL-17RA) and IL-17RC. The IL-17RA and IL-17RC are expressed on heart infiltrating macrophages in EAM mice models. It is shown that although developing EAM, IL-17A-deficient BALB/c mice do not acquire dilative cardiomyopathy at later time points (21). A recent study on hypoxia induced factor (HIF-1α) Knock-Out C57BL/6 mice showed that HIF-1α enhances Th17 development through direct transcriptional activation of RORγt, and activation of IL-17 promoter (22). On the other hand, hypoxia induced pathway can be activated by IL-17A and IL-17F, thereby maintaining an already established pathogenic

condition (23). In addition to hypoxia, inflammatory metabolites such as reactive oxygen species can trigger the HIF-1α response, which further affect T helper skewing towards Th17 (24). Since animal models and human studies suggest that hypoxic conditions increase vulnerability to AF, the interrelation between hypoxia and Th17 cells makes these cells the likely players in the pathogenesis of AF. Accordingly, in a study on a small group of elderly patients with paroxysmal AF, it was shown that inflammatory cytokine levels, including IL-17, decrease after intensive cholesterol lowering therapy (25). Therefore, IL-17 can be a key factor in the persistence of AF and complications related to the hypoxia and ischemic response.

In this study we investigated the serum level of IL-17A in patients with different types of Atrial Fibrilation compared with healthy controls. In addition, the correlation between serum levels of CCL5 and CCL18, which increase in the sera of patients with unstable angina pectoris (UAP) during cardiac ischemia, with IL-17A was assessed (26). To the best of our knowledge, there is currently no report on these parameters together in the AF condition.

MATERIALS AND METHODS

Subjects. In a case-control study between June 2011-June 2013, blood samples were collected from 133 patients (64 females and 69 males) who were diagnosed with Atrial Fibrillation (AF) and 107 healthy individuals (21 females and 86 males). The patients and controls were recruited via convenient method of sampling. This study was approved by the Ethics Committee of Shiraz University of Medical Sciences. The patients were informed about the aim of the study as well as safety and security measures before their consents were obtained.

Of the 133 patients who entered this study, 38 were presented with paroxysmal AF, 46 presented persistent AF, and 49 presented permanent AF. Atrial Fibrilation was diagnosed by ECG findings and patient's symptoms. Patients were categorized into paroxysmal, persistent, and permanent according to the European Society of Cardiology Guideline 2010. Briefly, paroxysmal AF was established as a self terminating attack of faulty electrical signals and increased heart rate symptoms within 48 hrs; persistant AF was identified if the abnormal heart rhythm lasted more than a week or needed intervention to be terminated, and permanent AF was accepted by patient and physician to treat only by rate control. The inclusion criteria for the patients were a confirmed diagnosis of AF and no history of electric shock therapy, while the cases with a lack of consent to enter the study or a history of cardiogenic shock, anti-inflammatory treatment, autoimmune and inflammatory diseases such as Rheumatoid Arthritis, SLE, Malignancy, Chronic Renal Failure, and Acute Coronary Syndrome were excluded from the study. The differential count of white blood cells as well as clinical findings for patients was also recorded at the time of sampling. The patients' clinical criteria and the prescribed medications are shown in Table 1.

Healthy individuals were entered into the study based on an informed consent, matching age with the patients, and lack of history of any cardiovascular and inflammatory diseases. The mean age of patients was 63.92 ± 17.02 yrs, and the mean age of healthy individuals was 57.62 ± 10.57 yrs.

ELISA: IL-17A concentration was measured in the sera of 112 patients who met the inclusion criteria and 107 healthy individuals using a commercial Biotin/Avidin based

Sandwich ELISA (eBiosciences, USA). For a subgroup of patients who had elevated IL-17A in their sera (> 1 Pg/ml; n=26), the levels of CCL5 and CCL18 were also measured using commercial ELISA assays (R&D Systems Europe, UK, and Cell Sciences, USA, respectively).

Table 1. Clinical Characteristics of patients.

Variables	
Age, years (Mean ± SD)	63.92 ± 17.02
BMI, kg/m2 (Mean ± SD)	25.08 ± 4.42
Heart rate, bpm (Mean ± SD)	94.89 ± 24.27
CAD, n (%)	40 (35.71)
Hypertension, n (%)	77 (68.75)
Hyperlipidemia, n (%)	37 (33.04)
Diabetes Mellitus, n (%)	30 (26.79)
Smoking, n (%)	35 (31.25)
BBB, n (%)	40 (35.71)
LVEF, % (range)	48.2 (15-60)
LA Diameter, cm (Mean ± SD)	4.55 ± 0.9
LVDD, cm (Mean ± SD)	5.18 ± 0.71
LVSD, cm (Mean ± SD)	3.61 ± 0.86
LVH, n (%)	18 (16.07)
Statin, n (%)	38 (33.93)
Steroid, n (%)	4 (3.57)
Warfarin, n (%)	35 (31.25)
ASA, n (%)	44 (39.29)
Beta-blocker, n (%)	68 (60.71)
Plavix, n (%)	11 (9.82)
ACE inhibitor, n (%)	44 (39.29)
NSAID, n (%)	3 (2.68)
RF, n (%)	3 (2.68)
PCI, n (%)	6 (5.36)
CABG, n (%)	15 (13.39)
NLR (Mean ± SD)	6.04 ± 5.77
MLR (Mean ± SD)	0.20 ± 0.17
Platelet, $\times 10^6$/L (Mean ± SD)	212 ± 75
Neutrophil, %	73.2
Monocyte, %	3.4
Lymphocyte, %	20.8

Statical Analysis: Student's *t-test* was used for analysis of parameters between case and control groups. One-way ANOVA was used for comparisons between more than two groups. When the data points were less than 30 in each category, normality of data was checked and parametric or non-parametric (Kruskal-Wallis and Mann-Whitney) analyses were done. Pearson or Spearman correlation tests were used to investigate bivariate correlations. All the analyses were performed using SPSS software (11.5, Chicago, Illinois). Statistically significant differences were defined as comparisons resulting in $p<0.05$.

RESULTS

Mean IL-17A levels in patients was found to be 1.28 ± 3.5 Pg/ml compared to 0.19 ± 0.64 Pg/ml in healthy subjects (Figure 1). In total, 80 patients (out of 112) and 25 controls (out of 107) were found to have detectable IL-17A in their sera.

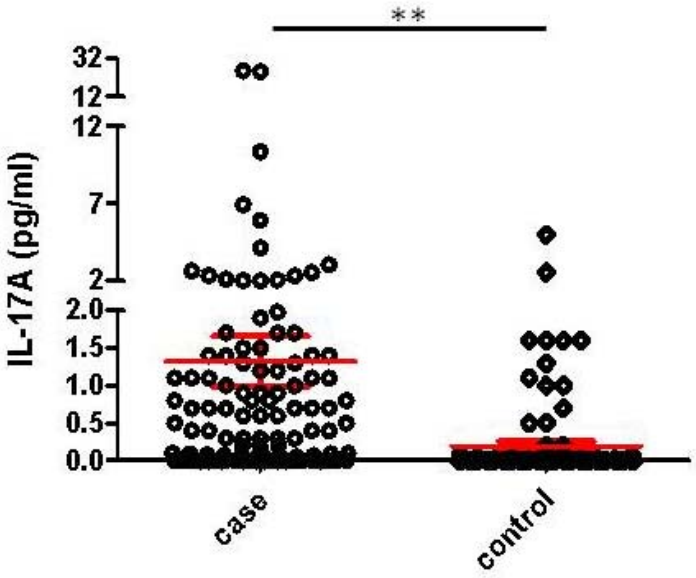

Figure 1. Comparison of IL-17A levels between patients with AF and healthy controls. Each circle is representative of IL-17A in each individual. Mean ± SD is shown.

The differences in the mean ($p=0.001$) and frequency were found to be statistically significant (69.6% vs. 23.4%, $p<0.001$, respectively). IL-17A levels tended to increase in the persistent and permanent AF (more than two-fold increase) compared to paroxysmal AF. However, the difference did not reach the significant level. Table 2 demonstrates the mean of IL-17A in sera of patients with paroxysmal, persistent and permanent AF.

While the serum level of IL-17A was marginally increased in smoker vs. non-smoker patients ($p=0.06$), there was a significant increase in the level of IL-17A in smoker

patients compared to smoker controls (p=0.0002, Supplementary Figure 1).
The difference in the level of IL-17A in sera of non-smoker patients and non-smoker controls did not reach the significant level (p=0.09).

Table 2. Comparison of IL-17A in sera of patients with paroxysmal, persistent and permanent AF.

	N (%)	IL-17A (Pg/ml)	
AF groups	**112 (100)**	**Mean ± SD**	**P value**
Paroxysmal	24 (21.4)	0.62 ± 0.79	
Persistent	42 (37.5)	1.46 ± 4	0.87
Permanent	46 (41.1)	1.52 ± 3.54	

Interestingly, there was a significant elevation in the level of IL-17A in the patients with a history of coronary artery bypass graft (CABG) compared with the patients without such history (Mann Whitney test, p=0.01; Figure 2).

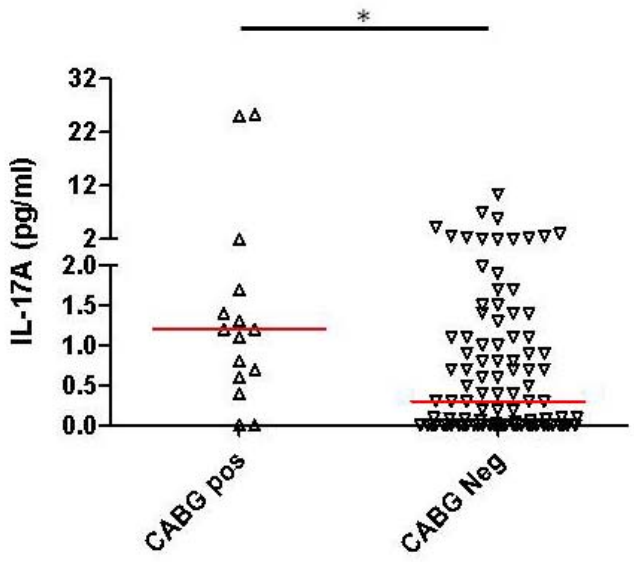

Figure 2. An increase in the IL-17A levels in cases with a history of CABG is shown. The triangles are representative of patients. Median is shown on the graph.

Table 3 represents the mean of IL-17A in the patients with and without CABG. We also noticed that 13 out of 15 patients in the CABG+ group were positive for IL-17A as well. The average time after surgery for the patients with a history of CABG was 59.4 ± 51.7 months. There was no correlation between the time after CABG and IL-17A levels

(Supplementary Figure 2). Although the IL-17A level in sera of patients with left ventricular hypertrophy (LVH), ST depression, moderate Aortic Insufficiency (AI), Grade III diastolic dysfunction (DD), higher than 100 bpm rate, LVEDD+, and moderate and severe mitral regurgitation (MR) was found to be increased, these differences did not reach the significant level (Supplementary Table 1).

Table 3. IL-17A levels in sera of patients with and without CABG.

	N (%)	IL-17A (Pg/ml)	
CABG groups	**112 (100)**	**Mean ± SD**	**P Value**
Yes	15 (13.4)	4.19 ± 8.55	0.018*
No	97 (86.6)	0.86 ± 1.52	

* Mann-Whitney test

There were no significant differences between the IL-17A levels in patients with high blood pressure (Systolic ≥14 or Diastolic ≥90 mmHg) compared to those with a normal BP (1.32 ± 3.37 vs. 1.27 ± 3.82 Pg/ml). The same was observed for diabetic (1.4 ± 4.77 Pg/ml) compared to non-diabetic (1.29 ± 3.13 Pg/ml) patients.

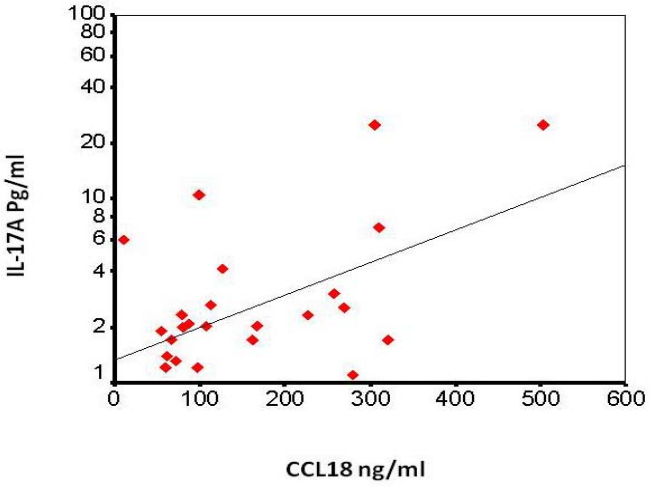

Figure 3. Correlation between IL-17A levels and CCL18 in the sera of patients with AF. The diamonds are representative of patients with elevated serum IL-17A (>1 pg/ml). Spearman's Rho=0.6, p=0.001; n=26

In patients with elevated IL-17A, the levels of CCL5 and CCL18 were measured (n=26). Interestingly, a statistically significant positive correlation between IL-17A concentration and CCL18 was found (R=0.6, p=0.001; Figure 3).

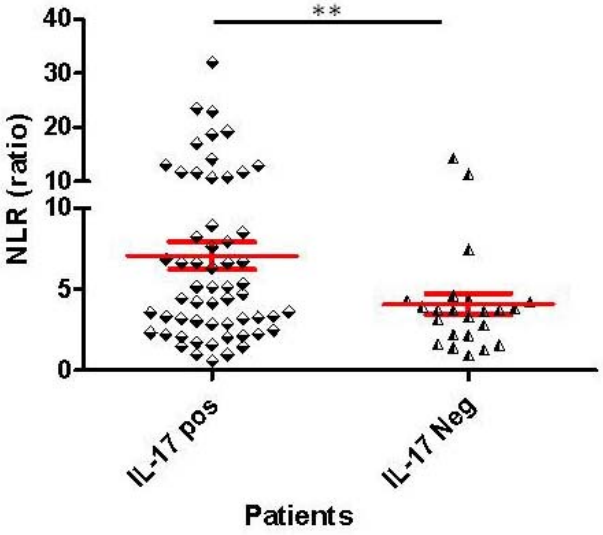

Figure 4. Comparison of Neutrophil/Lymphocyte Ratio (NLR) between patients with and without detectable IL-17A in their circulation. Higher NLR was observed in patients who had IL-17A in their circulation. Mean ± SD is shown.

Moreover, an increase in the Neutrophil/Lymphocyte Ratio (NLR) was observed in patients with circulating IL-17A compared to other patients (7.1 ± 6.4 % vs. 4.1 ± 3.15%, p=0.006; Figure 4).

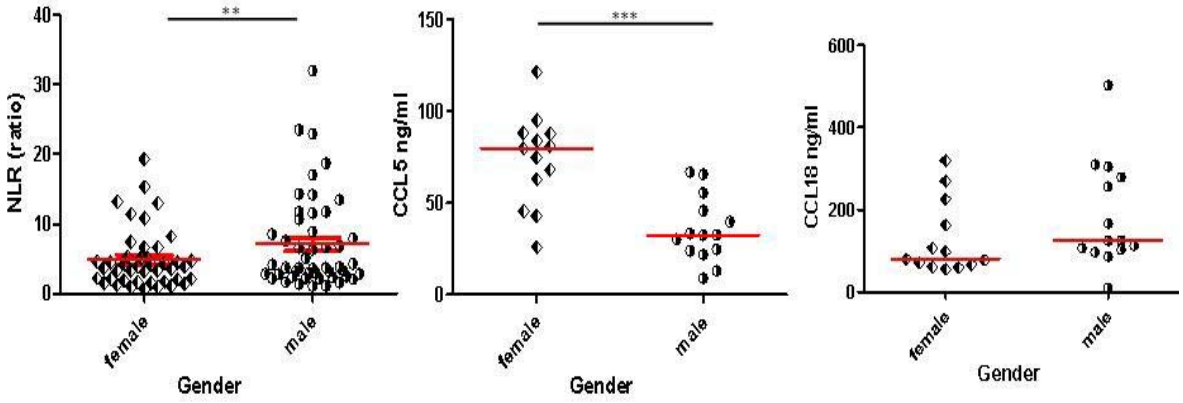

Figure 5. Comparison of Neutrophil/Lymphocyte Ratio (NLR), CCL5, and CCL18 between genders. Higher NLR and lower CCL5 concentration were observed in male patients compared to female patients. The red lines on the graphs show mean ± SD (NLR) or median (CCL5 and CCL18) of the data.

The male patients showed higher increase in NLR (9.8 ± 7.9 % vs. 2.9 ± 2.02 %, p=0.007) which was accompanied by a decrease in CCL5 (35. 40 ± 17.7 vs. 73.66 ± 24.98 ng/ml, p=0.000), a marginal increase in CCL18 (184.81 ± 129.67 vs. 127.50 ± 88.96 ng/ml, p=0.085) and a significant decrease in the platelet count (181 ± 85 vs. 247 ± 82 $\times 10^6$/L; Mann Whitney test, p=0.02) compared to females (Figure 5). However, we did find a significant difference in the platelet count between male (200 ± 78 $\times 10^6$/L) and female (224 ± 70 $\times 10^6$/L) patients in total (p=0.6).
There was a correlation between NLR and Monocyte/Lymphocyte Ratio (MLR) as well (R=0.58, p=0.001; Supplementary Figure 3). There was an increase in the level of CCL5 in patients who were taking Acetylsalicylic Acid (ASA) (69.14 ± 28.63 vs. 44.81 ± 25.40 ng/ml, p= 0.046; Figure 6).

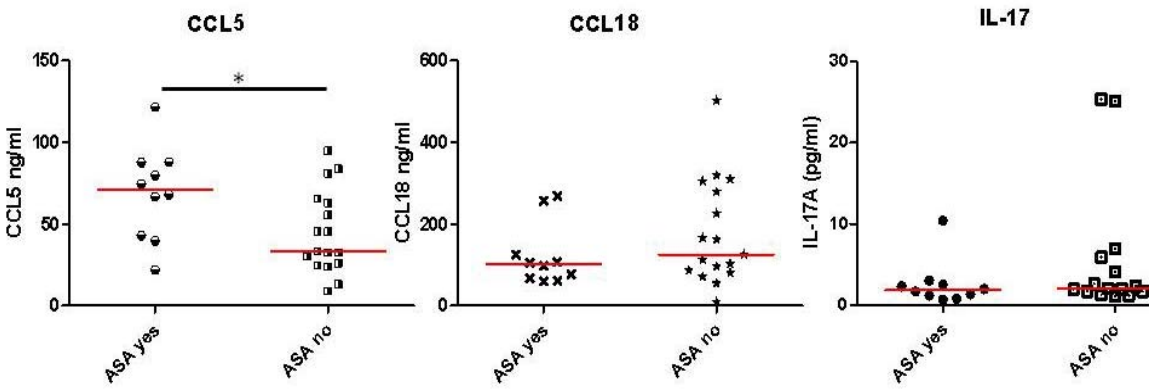

Figure 6. Comparison of CCL5, CCL18, and IL-17A between patients based on ASA therapy. Higher levels of CCL5 in patients receiving Acetylsalicylic Acid (ASA) compared to those who did not. The red line on the graphs shows median of data.

A non-significant trend of correlation between platelet count and CCL5 was also observed in the group of 26 patients (Spearman's Rho=0.326, p=0.104; Supplementary Figure 4). No difference was observed in the IL-17A levels as well as IL-17A positivity, when other clinical criteria were taken into consideration.

DISCUSSION

In the current study, we found that IL-17A is elevated in the sera of patients with AF. Like many other diseases, an altered level of circulating cytokines is a hallmark of heart diseases. Cytokines are considered as possible therapeutic targets or biomarkers in cardiovascular diseases, and such approaches are currently under investigation in animal models (4). IL-17A has been suggested to be a critical effector cytokine, responsible for experimental autoimmune myocarditis, and its neutralization reduces myocarditis and heart autoantibody responses (27). Moreover, an increase in the IL-1, IL-6 and IL-17A inflammatory cytokines has been shown in an isoproterenol (ISO) induced heart failure

(HF) rat model (28). IL-17A contributes to myocardial fibrosis in isoproterenol-induced HF through regulation of the RANKL/OPG and MMP/TIMP systems. The RANKL/OPG system is one of intermediaries between IL-17A and MMP-1 in cardiac fibroblasts. Therefore, anti-IL-17A treatment is a potential therapeutic strategy in HF (29). Accordingly, using a rat monoclonal anti-IL-17 in a mice model of viral myocarditis showed that neutralization of IL-17 can improve clinical symptoms, subside disease course, and decrease serum IL-17 level (30).

Our results indicated a non-significant increase in the level of IL-17A in the sera of smoker patients compared to non-smoker patients. Although cigarette smoking may have contributed to the inflammatory conditions and accelerated IL-17A, the observation that smoker patients had significantly elevated IL-17A compared to the smoker controls shows that smoking, per se, is not a direct contributor to IL-17A production. Indeed, both smoking and IL-17A increase the risk of thromboembolism and fatality in AF patients (31,32). The augmented increase in IL-17A levels in the AF patients with a history of CABG may also underline the common pathogenic inflammatory mechanisms in both conditions.

IL-17A is a major cytokine in the induction of PMN proliferation and recruitment through GM-CSF and CCL7, CCL2, CXCL8, CXCL5, CXCL1 chemokines. In our study, the NLR was increased in patients with circulating IL-17A and this increase correlated with MLR and monocyte count. It has been shown that in inflammatory conditions neutrophils as well as monocytes/macrophages are the cellular sources of CCL18 (33). These inflammatory leukocytes further produce Matrix Metalloproteinases among which MMP13, MMP9, MMP3, MMP1 are produced under stimulation of IL-17A (34, 35). Destruction of extracellular matrix by MMPs results in the infiltration of leukocytes to the inflamed tissue and also increased the production of TGF-β, which in turn increases atrial fibrosis and alteration in electrical signals (36). CCL18 itself can also activate fibroblasts and contribute to the pathogenic fibrosis process (37).

Previous studies have shown that a major source of plasma CCL5 is platelet and the decreased platelet counts in immune thrombocytopenic purpura correlates with the levels of CCL5 in these patients (38). Although gender differences are previously reported to affect the aggregation of platelets and thereby their clearance by liver macrophages, the decrease of CCL5 and platelet counts in male patients, who had elevated IL-17A, cannot be totally related to their gender, as we did not see any difference in the platelet counts between male and females in total, i.e. those with and without elevated IL-17A (39,40). We also observed that the level of CCL5 chemokine in patients who were treated by anti-coagulant ASA therapy was only marginally correlated with platelet count. Interestingly, 70% of ASA-treated patients and only 37% of those who did not receive ASA were females. The relieving effect of non-steroidal cyclooxygenase inhibitors on the level of CCL5 in the sera of women who underwent total abdominal hysterectomy has already been investigated (41). The significance of CCL5 increase in the context of cytokine milieu during AF chronic inflammation and its correlation with gender, need to be addressed in further investigations.

In summary, our study sheds light on the complex interplay between inflammation and AF. We observed that there is an increase in the IL-17A immune inflammatory cytokine in different types of AF along with correlation with CCL5, CCL18, and NLR ratio in the blood. The production of IL-17A by Th17 cells, which are mainly memory or effector cells of the adaptive immunity, makes this cytokine a unique player outside the range of innate inflammation. IL-17A is a main neutrophil attractant, which is already

known as the contributor in AF related inflammation. Therefore, IL-17A and its receptor may be considered as new therapeutic targets in Atrial Fibrillation. Different humanized monoclonal antibodies against IL-17 and its receptor are currently under evaluation in clinical trials for treatment of rheumatoid arthritis and psoriasis (42, 43). Therefore, there may be a promising approach for immune-therapeutic interventions in AF condition.

Supplementary information

Supplementary Figures 1 and 2, and Supplementary Table 1.
http://iji.ir/december2014/3rdiji_vol11_no4_2014_Supplementary_Material.pdf

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