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The Role of Inflammation and Oxidative Stress in Atrial Fibrillation

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Abstract

BACKGROUND—Atrial fibrillation (AF) is the most common arrhythmia in clinical practice. There is increasing evidence that inflammation and oxidative stress contribute to the pathogenesis of AF, but their role remains poorly defined. Furthermore, it is unclear if inflammation and oxidative stress are associated with particular types of AF.

OBJECTIVE—The purpose of this study was to define the role of inflammation and oxidative stress in AF.

METHODS—Using a case-control study design, 305 patients with AF were compared to 150 control patients. AF was categorized into lone and typical AF, and further sub-categorized as paroxysmal, persistent or permanent AF. Serum concentrations of interleukin (IL)-6, IL-8, IL-10, tumor necrosis factor (TNF)- α , monocyte chemotactic protein (MCP)-1, vascular endothelial growth factor (VEGF) and N-terminal pro-brain natriuretic peptide (NTpBNP) and urinary F₂-isoprostanes, a measure of oxidative stress, were measured.

RESULTS—IL-6, IL-8, IL-10, TNF- α , MCP1, VEGF and NTpBNP concentrations were independently associated with AF (all P values <0.05), but F₂-isoprostane excretion was not elevated (P=0.50). There was a graded increase in TNF- α (median [interquartile range (IQR)]: 6.8 [3.4–11.3], 8.0 [5.6–10.9], 10.1 [5.7–12.4] pg/ml, P<0.05) and NTpBNP (170.6 [67.3–481.9], 681.39 [310.3–1439.0], 1179.9 [653.1–2096.0] pg/ml, P<0.001) among the subgroups of paroxysmal, persistent and permanent AF, respectively.

CONCLUSIONS—This study shows that inflammatory biomarkers were significantly increased in patients with AF, supporting a strong association between inflammation and the arrhythmia. Surprisingly, urinary F₂-isoprostanes, a sensitive index of systemic oxidative stress in vivo, were not increased in AF overall, or in different subtypes of AF.

Keywords

Atrial fibrillation; inflammation; cytokines; oxidative stress; F₂-isoprostanes

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice and contributes to impaired quality of life, and increased morbidity and mortality.^{1–4} The long-term maintenance of sinus rhythm in patients with AF remains a challenge because of the adaptive changes that occur, commonly termed electrical and structural remodeling. The mechanisms underlying both the initiation and perpetuation of AF are not well established but are thought to involve inflammation and oxidative stress.^{5–7}

Several lines of evidence support a strong association between inflammation and the pathogenesis of AF. Inflammatory infiltrates, myocyte necrosis and interstitial fibrosis were found in atrial tissue from patients with idiopathic or ‘lone’ AF but not in control patients.^{3; 8–10} Furthermore, a number of studies have shown that concentrations of inflammatory mediators or markers, such as IL-6 and high-sensitivity C-reactive protein (hs-CRP), are increased in patients with AF.^{5;8;11–13} One mechanism that may mediate the effects of inflammation in AF is oxidative stress.

Emerging evidence implicates oxidative stress in the initiation and maintenance of AF.¹⁴ Carnes *et al* have shown that AF induced by rapid pacing in dogs decreases tissue ascorbate levels and increases protein nitration, a marker of oxidative and nitrosative stress.¹⁵ Biochemical evidence of oxidation by peroxynitrite and hydroxyl radicals, both downstream products of oxygen radical generation, has also been demonstrated in experimental models of AF.¹⁶ Coronary artery bypass surgery, a procedure often complicated by AF, is associated with an increase in oxidized glutathione and lipid peroxidation.^{17–20} However, *in vivo* studies have been difficult to perform because of the lack of reliable methods to quantify oxidative stress. Although a number of assays are available, they are primarily of use to measure oxidation *in vitro* and are inaccurate when applied to the *in vivo* assessment of oxidative stress in humans.²¹ Recently, the development of methods to quantify F₂-isoprostanes (IsoPs), prostaglandin-like compounds derived from the free radical-catalyzed peroxidation of arachidonic acid, has allowed a facile and accurate assessment of oxidative stress *in vivo*.^{19;22}

Although inflammation and oxidative stress are both considered to be potential initiators and mediators of AF, few studies have evaluated their role in AF generally, and in different types of AF specifically. Thus, we hypothesized that measures of inflammation and oxidative stress are increased in AF. Furthermore, we also hypothesized that indices of inflammation and oxidative stress are lower in patients with lone AF compared to typical AF, and in patients with paroxysmal AF compared to those with persistent and permanent AF.

Methods

Study population

Between November 2002 and October 2006, subjects with AF were prospectively enrolled in the Vanderbilt AF Registry, which comprises clinical and genetic databases.²³ At enrollment a detailed medical and drug history was obtained. Patients with AF were recruited from the Vanderbilt Cardiology and Arrhythmia Clinics, the emergency department, and in-patient services. Individuals of age older than 18 years with a diagnosis of AF, confirmed by electrocardiogram (ECG), who presented because of symptoms or who were diagnosed during a routine physical examination were included in the AF Registry. Subjects were excluded if AF was diagnosed in the setting of recent cardiac surgery or they were unable to give informed consent or return for follow-up. The control group consisted of 150 subjects with no known inflammatory disease or history of arrhythmias. The study protocol was approved by the Institutional Review Board of Vanderbilt University and participants were enrolled following informed written consent.

Definitions

For the purposes of our study, AF was defined as replacement of sinus P waves by rapid oscillations or fibrillatory waves that varied in size, shape, and timing and were associated with an irregular ventricular response when atrioventricular conduction was intact. Documentation of AF on an ECG, rhythm strip, event recorder, or Holter monitor recording was necessary. Lone AF was defined as AF occurring in individuals ≤ 65 years of age without hypertension, diabetes, heart failure (HF), coronary artery disease (CAD) or overt structural heart disease as determined by clinical examination, ECG and echocardiography within 2 years of the onset of AF.²⁴ These patients were followed over time and as they age some developed inevitable comorbidities such as hypertension that they did not have at the time of onset of their lone AF. An echocardiogram was obtained on all patients at time of enrollment into the Registry. The upper limits of normal for cardiac chamber dimension were based on age and body surface area.

Paroxysmal AF was defined as AF lasting more than 30 seconds with spontaneous termination. Persistent AF was defined as AF lasting more than seven days and requiring either pharmacologic therapy or electrical cardioversion for termination. AF that was refractory to cardioversion or that was allowed to continue was classified as permanent.

Analysis of cytokines and isoprostanes

Measurement of inflammatory markers was performed in samples obtained at the enrollment visit for both patients with AF and control subjects. Venous blood was obtained and serum obtained by centrifugation at 4°C for 10 min at 4000 rpm within 2 hours of collection. The serum sample was stored at -80°C until analysis. Serum IL-6, IL-8, IL-10, tissue necrosis factor alpha (TNF α), monocyte chemoattractant protein-1 (MCP-1), vascular endothelial growth factor (VEGF) and N-terminal-pro-brain type natriuretic peptide (NTpBNP) were measured by multiplex enzyme-linked immunosorbent assay (Linco Research/Millipore Corp, St. Louis, MO). Urine samples for F₂-IsoPs were collected into aliquots and kept frozen at -80°C until analysis. Urinary F₂-IsoPs were quantified using gas chromatography and mass spectroscopy as previously described and expressed as ng/mg creatinine (ng/mg Cr).²⁵ All biomarkers measured were selected as a priori in this study.

Statistical analysis

Data are expressed as median (interquartile range [IQR]) or frequency (percentage). Baseline characteristics were assessed using the Wilcoxon rank sum test or Kruskal-Wallis test for continuous variables and chi-square tests for categorical variables. Values below the detectable concentration of IL-6, IL-8, IL-10, TNF- α , MCP-1, VEGF, NTpBNP were left-censored for each assay. Consistent with previous cytokine studies, most of the cytokine results are skewed. Therefore, parametric survival models with left censoring were used to evaluate the adjusted group differences in various biomarkers assuming log-normal distribution after adjusting for age, sex, race, body mass index (BMI), heart failure (HF), and statin use. The group differences of interest included comparisons between control and AF groups, typical and lone AF groups, as well as paroxysmal, persistent, and permanent AF groups. All statistical analyses were performed with use of R 2.8.1 (www.r-project.org). A two-sided p value less than 0.05 was considered statistically significant. Since multiple hypotheses and endpoints were analyzed in this study, separate analysis for each hypothesis were conducted and reported for both negative and positive results in the pre-specified priority order. Therefore, no multiplicity corrections were made for the number of endpoints in various comparisons.

Results

AF and control groups

The clinical characteristics of the control population are provided in Table 1. The control group had a median age of 49 years (IQR, 39–56 years), and had more female subjects (72%) than the AF group. BMI (30.2 vs. 26.6 kg/m²) and statin use (50% vs. 11%) were significantly higher in patients with AF as compared with the control group. The clinical characteristics of patients with AF (n = 305) (including both typical and lone AF) are representative of an outpatient population with the arrhythmia referred to a tertiary referral center. As expected, patients with lone AF were younger and had lower body mass index (BMI), whereas in those with typical AF, statin use, hypertension, diabetes, HF, left atrial size and reduced left ventricular ejection fraction were significantly more common.

Table 2 compares the concentrations of biomarkers in the AF group overall, and in the subset with lone AF, with those in control subjects. Serum concentrations of IL-6, IL-8, IL-10, TNF- α , MCP-1, VEGF, and NTpBNP were significantly higher in patients with AF than controls, after adjusting for age, sex, race, BMI, heart failure and statin use. However, concentrations of urinary F₂-IsoPs were similar in the control and AF groups (1.75 [AF] vs. 1.84 [control] ng/mg/Cr; P=0.50). When comparing the lone AF and the control groups, serum concentrations of IL-8, TNF- α , MCP-1, VEGF and NTpBNP were significantly higher in patients with lone AF after adjusting for age, sex, race, BMI and statin use, but concentrations of urinary F₂-IsoPs did not differ (Figure 1). In addition, there was no significant difference in urinary F₂-IsoPs levels in those patients with and without valvular heart disease (VHD) (1.82 [1.29–2.40] (n=60) vs. (1.70 [1.24–2.60] ng/mg/Cr, (n=237), P=0.69). Male patients in the control group had lower urinary F₂-IsoPs (men, 1.46 [1.0–1.95] ng/mg/Cr (n=42) vs. women, 2.01 [1.32–3.19] ng/mg/Cr (n=108), P<0.001) as well as in the typical AF group (men, 1.62 [1.21–2.16] ng/mg/Cr (n=205), vs. women 2.16 [1.39–3.44] ng/mg/Cr (n=100), P<0.001). In further analysis (table 3), there was no significant difference in urinary F₂-IsoPs and inflammatory markers between the patients with AF receiving statins (n=151) and those who were not taking statins (n=154) in the total AF group adjusting for age, gender, BMI, HTN, CAD and heart failure (all P values > 0.05).

Lone and typical AF comparison

Table 4 shows the biomarker concentrations in patients with lone AF (n=68) and those with typical AF (n=237). Before adjustment, serum concentrations of IL-10, TNF- α and NTpBNP were significantly higher in patients with typical AF compared to lone AF, however, this trend was not significant after adjusting for age, race, sex, BMI, HF, and statin use. Urinary F₂-IsoPs were not significantly different in the two groups (1.7 [typical AF] vs. 1.77 [lone AF] ng/mg Cr; P>0.05).

Biomarkers and oxidative stress in subtypes of AF

Patients were categorized as having paroxysmal AF (n=157), persistent AF (n=105) and permanent AF (n=39). There were no significant differences in urinary F₂-IsoPs, or serum IL-8, MCP-1 and VEGF concentrations in the three subtypes of AF after adjusting for age, sex, race, BMI, HF, and statin use (Table 5). However, IL-10, TNF- α and NTpBNP concentrations were significantly higher in both persistent and permanent AF patients as compared to those with paroxysmal AF (P=0.03, 0.01, and <0.001, respectively). Concentrations of IL-6 were significantly higher in patients with persistent and paroxysmal AF compared to those with permanent AF (P=0.05). Furthermore, there was a graded increase in the NTpBNP levels with the duration and type of AF (1179.95 pg/ml [permanent] > 681.39 pg/ml [persistent] > 170.62 pg/ml [paroxysmal]). (Table 5.)

Discussion

Recently, evidence has emerged implicating inflammation and oxidative stress in the pathogenesis of AF.^{2;14;26–28} We have not only shown that inflammatory markers were associated with AF but also that elevated inflammatory mediators varied according to the different sub-types of the arrhythmia. Surprisingly, in the same large cohort of patients with this common arrhythmia, levels of urinary F₂-IsoPs, a sensitive index of oxidative stress *in vivo*, were not increased.

In this study, we measured a panel of inflammatory biomarkers in a large cohort of patients with lone and typical AF. In unadjusted analysis we found that patients with typical AF had significantly elevated serum concentrations of IL-10, TNF- α and NTpBNP when compared to those with lone AF. This is not unexpected as patients with typical AF are more likely to have co-existing co-morbidities such as hypertension and HF that would tend to elevate inflammatory mediators. In contrast, patients with lone AF have no overt structural heart disease and thereby are less likely to have elevated concentrations of biomarkers. Thus, after adjusting for variables known to modulate inflammation (age, sex, race, BMI, HF and statin use) there were no significant differences in concentrations of inflammatory markers between patients with lone AF and typical AF (Table 4). IL-6 concentrations were significantly higher in the total AF group than in control subjects but did not differ between lone AF and controls (P=0.12). IL-6 concentrations were significantly lower in permanent AF than paroxysmal and persistent AF (P=0.048). On the other hand, TNF concentrations were highest in patients with permanent AF. It is not clear why IL-6 was lower in permanent AF, but in animal models and human cardiac myocytes IL-6 expression was differentially regulated and was strongly associated with comorbidities and such factors could contribute to this observation.^{29;30}

Lone AF patients provide a unique opportunity to examine the relationship between inflammation and the arrhythmia independent of the contribution of underlying heart disease. Ellinor et al performed a similar analysis comparing hs-CRP levels between patients with lone and typical AF and found no significant difference.¹³ Although one group reported that lone AF is associated with mild fibrillar loss, myocyte hypertrophy and increased mitochondria in the atrial tissue,³¹ the precise role of inflammation in the pathogenesis of AF still remains unclear. Our findings suggest that patients with lone AF have marked elevations of inflammatory markers; therefore AF increases inflammation or an inflammatory substrate predisposes to AF.

Although oxidative stress has been implicated in the pathophysiology of AF, prior studies have used less sensitive markers of oxidative injury.³² In this study we measured urinary F₂-IsoPs *in vivo*, a reliable metric of oxidative stress. However, in our AF cohort, the levels of this sensitive marker of oxidative stress were not elevated compared to controls suggesting oxidative stress may not play a major role in the pathogenesis of the condition. However, there was a higher proportion of men in the AF group than in controls and men had lower F₂-IsoP concentrations than women and this difference in gender distribution could affect the comparison of AF and controls. To take account of this our statistical comparisons adjusted for gender and other baseline variables. There was no association between urinary F₂-IsoP levels and lone or typical AF and there was no correlation with the different sub-types of AF. While it has been shown that antioxidants may reduce post-operative AF rates by 2-fold,²⁸ whether oxidative stress is equally important in ambulatory AF remains to be determined.

Urinary F₂-IsoPs when measured by sensitive and specific methodologies using mass spectrometry, as was done here, are generally accepted as the gold standard for the measurement of lipid peroxidation and oxidative stress *in vivo*.³³ The Biomarkers of Oxidative Stress Study (BOSS) published in 2005, in fact, found that IsoPs were the most sensitive index

of endogenous oxidative stress when compared head-to-head with a variety of other oxidized lipid, protein, and DNA markers.³⁴

This study demonstrated that inflammatory markers or mediators are elevated in patients with lone AF lending support to the concept that inflammation plays an important role in the pathogenesis of the disease. A link between inflammation and AF, and its complications, has been established especially for hs-CRP and IL-6 levels in other studies.⁵ Although the precise mechanism(s) by which inflammatory markers provide prognostic information remains unclear, one possible explanation relates to the increased prothrombotic milieu that may increase the risk of vascular events.³⁵ Tissue factor production is stimulated by IL-6 and hs-CRP, and this might provide a mechanistic link between a prothrombotic state and increased vascular events. It is also worth mentioning that VEGF levels are significantly increased in AF patients, and as endothelial dysfunction is known to associate with AF, this may contribute to platelet activation and thrombosis.¹

In this study we showed that elevated inflammatory biomarkers are strongly associated with AF. Inflammation has important prognostic implications in AF; large prospective studies have shown that elevated hs-CRP levels correlated with risk factors for stroke and overall prognosis.¹ The positive correlation between elevated levels of TNF- α and NTpBNP and severity of AF suggests that these biomarkers could be prognostic markers for AF in clinical practice. Although studies assessing the efficacy of targeted anti-inflammatory therapy in AF prevention have provided conflicting results, our data support the concept that inflammation may play an important role in the pathophysiology of AF.

Study limitations

This study has a number of limitations. First, this was a cross-sectional study design and thus we only have inflammatory marker data at one time point, i.e., at enrollment into the AF Registry. Thereby the effects of pharmacotherapeutic agents such as statins known to modulate the inflammatory response could not be assessed longitudinally. The control subjects were enrolled to provide information about baseline levels of oxidative stress and cytokines in subjects without inflammatory disease for cardiovascular studies and were not specifically matched with the AF cohort. Although this may have resulted in differences in baseline characteristics, this was statistically adjusted for in our analyses. A second limitation relates to the fact that blood samples were not necessarily drawn when all patients were in AF. This might have biased the results to lower concentration of inflammatory markers. Furthermore, although we adjusted for various common confounding variables, it is possible that other additional variables, such as co-morbidities and anti-inflammatory medication use, may modulate inflammation and oxidative stress and this might have influenced our results. The differences of the characteristics between two groups can be minimized by adjustment but not neglected. Importantly, however despite the frequent use of statins and ACE inhibitors, inflammatory markers were elevated in patients with AF.

In addition, urinary F₂-IsoPs, provides a marker of overall systemic oxidative stress. Thus, it is possible that local or atrial oxidative stress may be increased and this effect may be diluted when analyzing systemic oxidative stress with measurement of urinary F₂-IsoPs. It would be interesting to explore how local atrial oxidative stress compares to systemic oxidative stress circulation, as well as the fluctuation of oxidative stress level immediately following AF. This type of invasive study that measures oxidative stress across the heart could only be done in a controlled environment, such as in patients undergoing cardiac catheterization or cardiac surgery.

Conclusion

This study has demonstrated that concentrations of inflammatory biomarkers were significantly increased in patients with AF and supports a strong association between AF and inflammation. Furthermore, elevated inflammatory markers in patients with lone AF suggest that inflammation is associated with AF independent of co-morbidities such as heart failure. Urinary F₂-IsoPs, a sensitive systemic index of oxidative stress *in vivo*, showed no significant differences between AF and control groups or among the subgroups of AF, suggesting that increased inflammation in AF is unlikely to be related to increased systemic oxidative stress.

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Figure 1. Biomarker concentrations in patients with lone AF and control subjects

Figures depict median (bold horizontal line in box), IQR (box) of biomarkers between controls and patients with lone AF.

Table 1

Clinical characteristics of patients with atrial fibrillation (AF)

	Control (n=150)	AF* (n=305)	Typical AF (n=237)	Lone AF† (n=68)	P-value‡	P-value§
Age (year)	49 (39–56)	62 (53–69)	64 (57–70)	53 (45–62)	<0.001	<0.001
Sex (male)	42 (28%)	205 (67%)	160 (68%)	45 (66%)	<0.001	0.84
White	119 (79%)	287 (94%)	223 (94%)	64 (94%)	<0.001	0.99
Body Mass Index (kg/m ²)	26.6	29.0	31.0 (27.7–36.1)	27.7 (25.6–31.5)	<0.001	<0.001
Statin use	16 (11%)	151 (50%)	131 (55%)	20 (29%)	<0.001	<0.001
Hypertension	44 (29%)	201 (66%)	185 (78%)	16 (24%) [‡]	<0.001	<0.001
Diabetes	5 (3%)	68 (22%)	66 (28%)	2 (3%) [‡]	<0.001	<0.001
Coronary Artery Disease	5 (3%)	76 (25%)	73 (31%)	3 (4%) [‡]	<0.001	<0.001
Stroke	0 (0%)	20 (7%)	16 (7%)	4 (6%) [‡]	<0.001	0.80
Heart Failure	0 (0%)	47 (15%)	47 (20%)	0 (0%)	<0.001	<0.001
Smoking (current)	21 (14%)	33 (11%)	27 (12%)	6 (9%)	0.36	0.60
Alcohol (current)	74 (49%)	143 (47%)	108 (46%)	35 (51%)	0.65	0.41
Left atrium size (mm)	----	43 (37–48)	43 (39–49)	39.5 (35–43)	----	<0.001
LVEF (%)	----	55 (52–60)	55 (50–60)	56 (55–62)	----	<0.001

* AF, atrial fibrillation;

† Values represent findings at enrollment into the AF registry. None of the patients with lone AF had hypertension, diabetes, heart failure, coronary artery disease or stroke within 2 years of the onset of AF.

‡ P values: control vs. AF overall;

§ P values: typical vs. lone AF;

Table 2

Biomarkers in patients with AF and control subjects.

Biomarker (pg/ml)	Control (n=150)	Total AF (n=305)	Lone AF (n=68)	P-value* (control Vs. total AF)	P-value* (control vs. lone AF)
Urinary F ₂ -IsoPs (ng/mg Cr)	1.8 (1.2–2.6)	1.8 (1.3–2.6)	1.7 (1.3–2.7)	0.50	0.17
IL-6 (pg/ml)	1.3 (0.3–13.8)	4.0 (1.6–10.0)	3.7 (0.6–15.6)	0.02	0.12
IL-8 (pg/ml)	3.2 (0.8–6.8)	8.5 (5.5–15.4)	7.4 (4.7–14.5)	<0.001	<0.001
IL-10 (pg/ml)	1.6 (0.4–4.0)	3.7 (1.0–6.6)	2.7 (0.6–5.0)	0.03	0.70
TNF- α (pg/ml)	1.4 (0.8–2.4)	7.8 (4.7–11.3)	6.9 (4.0–9.5)	<0.001	<0.001
MCP-1 (pg/ml)	117.2 (84.8–165.1)	233.0 (163.9–292.6)	242.3 (158.8–286.4)	<0.001	<0.001
VEGF (pg/ml)	26.4 (14.1–51.5)	76.6 (32.7–124.0)	90.6 (34.5–124.6)	<0.001	<0.001
NTpBNP (pg/ml)	24.6 (8.0–48.1)	386.7 (101.7–1075.9)	196.8 (72.0–738.2)	<0.001	<0.001

Data are presented as median (interquartile range, IQR.).

* P values represent comparison adjusted for age, sex, race, BMI, heart failure and statin use by the parametric survival model.

Table 3

Biomarker concentrations in AF patients on statin therapy compared to those AF patients not on statins

Biomarker (pg/ml)	No statin use (n =154)	Statin use (n =151)	P value*
Urinary F ₂ -IsoPs (ng/mg Cr)	1.8 (1.3–2.6)	1.6 (1.2–2.6)	0.95
IL-6 (pg/ml)	3.9 (1.6–11.3)	4.1 (1.6–9.5)	0.32
IL-8 (pg/ml)	7.5 (4.7–11.7)	10.1 (6.2–20.2)	0.49
IL-10 (pg/ml)	3.5 (0.6–6.2)	3.9 (1.5–7.5)	0.79
TNF- α (pg/ml)	7.4 (3.9–10.9)	8.3 (5.4–11.5)	0.75
MCP-1 (pg/ml)	229.7 (158.9–282.8)	234.6 (172.5–310.3)	0.76
VEGF (pg/ml)	85.1 (33.6–125.3)	71.7 (32.4–117.3)	0.85
NTpBNP (pg/ml)	316.3 (79.0–1074.7)	455.5 (178.2–1068.9)	0.67

Data are presented as median (IQR).

* Parametric survival model adjusting for age, gender, BMI, HTN, CAD and HF.

Table 4

Biomarker concentrations in patients with typical and lone AF.

Biomarker (pg/ml)	Typical AF (n =237)	Lone AF (n =68)	P value*
Urinary F ₂ -IsoPs (ng/mg Cr)	1.7 (1.3–2.5)	1.7 (1.3–2.7)	0.93
IL-6 (pg/ml)	4.1 (1.7–9.9)	3.7 (0.6–15.6)	0.81
IL-8 (pg/ml)	9.1 (5.7–15.5)	7.4 (4.7–14.5)	0.50
IL-10 (pg/ml)	4.1 (1.3–7.3)	2.7 (0.6–5.0)	0.07
TNF- α (pg/ml)	8.3 (5.0–11.7)	6.9 (4.0–9.5)	0.34
MCP-1 (pg/ml)	224.0 (164.4–293.6)	242.3 (158.8–286.4)	0.34
VEGF (pg/ml)	75.6 (32.7–123.2)	90.6 (34.5–124.6)	0.70
NTpBNP (pg/ml)	435.2 (122.9–1171.8)	196.8 (72.0–738.2)	0.73

Data are presented as median (IQR).

* Parametric survival model adjusting for age, gender, race, BMI, HF and statin use.

Table 5

Biomarkers concentrations in patients with different types of AF.

Biomarker (pg/ml)	Paroxysmal AF (n=157)	Persistent AF (n= 105)	Permanent AF (n=39)	P value *
Urinary F ₂ -IsoPs (ng/mg Cr)	1.6 (1.2–2.5)	1.9 (1.3–2.6)	1.8 (1.4–2.6)	0.59
IL-6 (pg/ml)	4.1 (0.7–12.6)	4.5 (2.2–9.9)	3.4 (2.0–7.3)	0.048
IL-8 (pg/ml)	8.2 (4.8–16.1)	9.7 (6.1–15.7)	7.4 (5.7–10.2)	0.37
IL-10 (pg/ml)	3.1 (0.5–6.2)	4.3 (1.5–7.1)	4.7 (2.3–7.6)	0.03
TNF- α (pg/ml)	6.8 (3.4–11.3)	8.0 (5.6–10.9)	10.1 (5.7–12.4)	0.007
MCP-1 (pg/ml)	234.6 (169.2– 298.0)	216.8 (153.6–281.5)	243.3 (183.7–292.7)	0.57
VEGF (pg/ml)	84.8 (32.1–130.3)	73.8 (38.3–118.1)	70.3 (28.6–107.6)	0.73
NTpBNP (pg/ml)	170.6 (67.3–481.8)	681.4 (310.3–1439.0)	1179.9 (653.1–	<0.001

* P value: Parametric survival model adjusting for age, race, sex, BMI, HF and statin 2096.0) use.