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Source of inflammatory markers in patients with atrial fibrillation†

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Aims Elevated levels of C-reactive protein and other inflammatory markers have been reported in some patients with atrial fibrillation (AF). Whether this finding is related to AF *per se* or to other conditions remains unclear. In addition, the source of inflammatory markers is unknown. Therefore, in the present study, we sought to assess the extent and the source of inflammation in patients with AF and no other concomitant heart or inflammatory conditions.

Methods and results The study group consisted of 29 patients referred for radiofrequency catheter ablation: 10 patients with paroxysmal AF, 8 patients with permanent AF, and 10 control patients with Wolf-Parkinson-White (WPW) syndrome and no evidence of AF (mean age 54 ± 11 vs. 57 ± 13 vs. 43 ± 16). No patient had structural heart diseases or inflammatory conditions. High-sensitive C-reactive protein, interleukin-6 (IL-6), and interleukin-8 (IL-8) were assessed in blood samples from the femoral vein, right atrium, coronary sinus, and the left and right upper pulmonary veins. All samples were collected before ablation. Compared with controls and patients with paroxysmal AF, patients with permanent AF had higher plasma levels of IL-8 in the samples from the femoral vein, right atrium, and coronary sinus, but not in the samples from the pulmonary veins (median values in the femoral vein: 2.58 vs. 2.97 vs. 4.66 pg/mL, $P = 0.003$; right atrium: 2.30 vs. 3.06 vs. 3.93 pg/mL, $P = 0.013$; coronary sinus: 2.85 vs. 3.15 vs. 4.07, $P = 0.016$). A high-degree correlation existed between the IL-8 levels in these samples (correlation coefficient between 0.929 and 0.976, $P < 0.05$). No differences in the C-reactive protein and IL-6 levels were noted between the three groups of patients.

Conclusion The normal levels of C-reactive protein and IL-6, along with the elevated levels of IL-8 in patients with permanent AF but not in those with paroxysmal AF, suggest a link between a low-grade inflammatory reaction and long-lasting AF. The elevated IL-8 levels in the peripheral blood, right atrium, and coronary sinus but not in the pulmonary veins suggest a possible source of inflammation in the systemic circulation.

Introduction

A growing body of evidence suggests a possible association between inflammation and atrial fibrillation (AF). Elevated plasma levels of C-reactive protein, a systemic marker of inflammation, and interleukin-6 (IL-6), a pro-inflammatory cytokine, have been reported in patients with both paroxysmal and persistent AF,[1–6] with higher C-reactive protein levels in the latter group.[1,2] Furthermore, C-reactive protein was found to predict successful restoration of sinus rhythm but also the relapse of AF in patients undergoing direct current (DC) cardioversion.[7,8] Also, expression of interleukin-8 (IL-8) mRNA was reported in atrial samples from some patients with permanent AF.[9] The significance of these findings, however, remains unclear. They may express an inflammatory state related to AF itself or to other conditions that are often associated with AF, such as heart failure, coronary artery disease, or diabetes mellitus.[10–12]

The source of inflammatory markers in these patients is also unclear. Electrophysiological studies have shown that most paroxysms of AF are initiated by rapid focal arrhythmias originating in the region of the pulmonary veins.[13,14] Inflammatory changes have been reported in the atria in some patients with focal tachycardias.[15] Also, atrial biopsy

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specimens in some patients with idiopathic paroxysmal AF refractory to anti-arrhythmic therapy showed marked inflammatory infiltrates, myocyte necrosis, and fibrosis.[16] In view of these findings, it could be speculated that inflammatory mechanisms involving the atria and/or the region of the pulmonary veins might trigger focal tachyarrhythmias and induce pro-arrhythmic structural and electrical changes that could increase the propensity to AF in these patients.[15,17–19] These mechanisms could reflect local or widespread inflammatory processes.

Therefore, we conducted a pilot study to assess the extent and possible source of inflammation in patients with AF. The study aimed at assessing inflammatory markers in the heart and in the systemic and pulmonary circulation in patients with paroxysmal and permanent AF referred for catheter ablation. In order to minimize the possible confounding effect of other disorders, we included only patients with AF and no other concomitant heart and inflammatory conditions.

Methods

Study population and patient selection

We studied 18 patients with AF and no concomitant structural heart disease: 10 patients with paroxysmal AF (at least 1 episode per month), refractory to at least 1 anti-arrhythmic drug, and 8 patients with permanent AF (continuous AF for at least 2 months). The control group included 10 patients with WPW syndrome due to left-sided accessory pathways, with no clinical and ECG evidence of AF and no structural heart disease. All patients were referred to our institution for radiofrequency catheter ablation due to symptomatic arrhythmias. Exclusion criteria were previous cardiac surgery or percutaneous catheter ablation within 90 days, history of infection within 90 days, structural heart disease, diabetes mellitus, neoplasia, and use of lipid-lowering medication. All patients underwent standard history, physical examination, and routine laboratory tests. Transthoracic echocardiography was performed to rule out concomitant structural heart disease. The study protocol was approved by the Ethics committee for human research at the Linköping University, and all patients provided written informed consent.

Blood sampling and laboratory tests

The study was performed during routine cardiac catheterization prior to mapping and ablation. A 7-French (F) sheath (St Jude Medical, Minnetonka, MN, USA) was inserted into the right femoral vein. A 7-F left Amplatz catheter (Boston Scientific, Watertown, MA, USA) was introduced in the femoral vein, advanced into the right atrium and placed in the coronary sinus. Alternatively, cannulation of right atrium and coronary sinus was performed with an 8-F SL 1 transseptal sheath (St Jude Medical), advanced over a deflectable 7-F multipolar catheter (Biosense Webster, Diamond Bar, CA, USA) already placed in the coronary sinus. Blood samples from the femoral vein, right atrium, and coronary sinus were taken serially via the femoral venous sheath and the Amplatz catheter or the transseptal sheath. The left atrium was accessed through transseptal puncture. An intravenous bolus of heparin 100 IE/kg was administered after the transseptal puncture. Blood samples from the superior pulmonary veins were collected via the transseptal sheath advanced into the proximal segment of the sampled vein. After each sample was drawn, the sheath was flushed with heparinized sodium chloride. The first 5–10 mL of blood drawn for each sample was discarded to prevent contamination with flushing fluid.

The blood samples were centrifuged at 1000 *g* for 15 min, separated in aliquots and stored at -80°C until batch analysis. C-reactive protein was measured using the high-sensitive Roche Tina-quant® immunoturbidometric assay (Roche Diagnostics, Basel, Switzerland). High-sensitive enzyme-linked immunosorbent assay kits were used to measure IL-6 (R&D Systems Europe, Abingdon, UK) and IL-8 (Biosource International, Camarillo, CA, USA), according to the manufacturers' instructions. The lower limits of detection were 0.1 mg/L for C-reactive protein, 0.039 pg/mL for IL-6, and 0.1 pg/mL for IL-8. The circulating levels of IL-6 and IL-8 were assessed in blood samples from the femoral vein, coronary sinus, right atrium, and the upper pulmonary veins. Being synthesized mainly by the liver, C-reactive protein was determined only in samples from the femoral vein.

Statistical analysis

Normally distributed variables are expressed as mean $\pm$ SD. Plasma levels of inflammatory markers had a skewed distribution and are expressed as median and interquartile range. The AF patients were compared with the control group by means of one-way analysis of variance or Mann–Whitney test, as appropriate. Clinical parameters were compared using the χ^2 test. The correlation between plasma levels of inflammatory markers at different locations was assessed by the Spearman rank correlation method. Regression plots of logarithmically transformed plasma levels of different inflammatory markers were also computed. A *P*-value of less than 0.05 was considered as statistically significant. All analyses were performed with JMP (JMP, version 5.1.1, SAS Institute Inc., Cary, NC) and Statview software (version 5.0, SAS Institute Inc., Cary, NC).

Results

Baseline patient characteristics

The patients' demographics, clinical characteristics, and anti-arrhythmic medication are detailed in *Table 1*. There were no significant differences between the three groups in any of the following variables: age, gender, body mass index, and history of hypertension. The mean duration of AF history was 6.6 years in the group of patients with paroxysmal AF and 5.8 years in the group with permanent AF. None of the AF patients or controls received steroid or non-steroid anti-inflammatory drugs. In addition, none of the patients or controls received cholesterol-lowering medication. The left atrial diameter assessed by echocardiography in the parasternal view was larger in AF patients than in controls ($P = 0.034$). Five patients with paroxysmal AF were in AF at the moment of blood sampling, whereas the remaining five patients were in sinus rhythm. Failure to cannulate the coronary sinus was encountered in three cases (two patients with paroxysmal AF and one control). Blood sampling from the pulmonary veins could not be achieved in one patient with paroxysmal AF.

Inflammatory markers

Median values and interquartile range of C-reactive protein, IL-6, and IL-8 obtained at the five sites sampled are presented in *Table 2*.

There were no differences between the patients with paroxysmal AF and controls in any of the inflammatory markers at any of the sampling sites. Neither the rhythm during blood sampling (i.e. sinus rhythm or AF) nor the duration of AF history or the presence of hypertension had any influence on these findings.

The patients with permanent AF and the controls had similar C-reactive protein levels. There was a trend for higher IL-6 levels in the samples from the pulmonary veins in the AF patients, although the difference did not reach statistical significance (*Table 2* and *Figure 1*). The IL-8

Table 1 Clinical characteristics of the study population

	Controls $n = 10$	Patients with paroxysmal AF $n = 10$	Patients with permanent AF $n = 8$	*P*-value
No. of subjects	10	10	8	
Age (years)	43 ± 16	54 ± 11	57 ± 13	0.081
Men	6 (60%)	8 (80%)	7 (88%)	0.369
Body mass index	27.10	26.87	26.21	0.469
Hypertension	0 (0%)	1 (10%)	3 (38%)	0.053
History of atrial fibrillation (years)	–	6.6 ± 3.9	5.8 ± 3.9	
Medication				
β-blockers	1 (10%)	7 (70%)	3 (38%)	
Ca-channel blockers	0 (0%)	1 (10%)	2 (25%)	
Digoxin	0 (0%)	0 (0%)	0 (0%)	
Propafenon/tambocor	0 (0%)	3 (30%)	0 (0%)	
Sotalol	0 (0%)	1 (10%)	0 (0%)	
Amiodarone	0 (0%)	2 (20%)	0 (0%)	
Left atrial diameter (mm)	38.2 ± 2.4	42.6 ± 6.6	43.2 ± 3.0	0.034
Atrial fibrillation during blood sampling	–	5 (50%)	8 (100%)	

Table 2 Inflammatory markers in the three groups of patients

	Controls	Patients with paroxysmal AF		Patients with permanent AF	
	$n = 10$	$n = 10$	*P*-value[a]	$n = 8$	*P*-value[b]
C-reactive protein (mg/L)					
Fe V	0.96 (0.55–1.62)	1.03 (0.38–2.65)	0.762	0.69 (0.51–6.83)	0.594
Interleukin-6 (pg/mL)					
Fe V	1.21 (0.66–2.62)	1.28 (0.86–2.27)	0.762	2.33 (1.03–6.70)	0.1551
RA	0.90 (0.52–1.66)	1.02 (0.63–1.73)	0.706	2.13 (0.93–5.27)	0.0914
CS	0.91 (0.36–1.91)	0.90 (0.77–1.90)	0.564	2.00 (0.82–5.29)	0.1152
LSPV	0.99 (0.53–1.98)	0.99 (0.70–1.83)	0.807	2.38 (0.90–5.06)	0.0506
RSPV	0.98 (0.61–1.89)	1.15 (0.73–1.76)	0.870	2.39 (0.91–5.19)	0.0832
Interleukin-8 (pg/mL)					
Fe V	2.58 (2.15–3.81)	2.97 (1.49–3.68)	0.940	4.66 (3.86–6.13)	0.003
RA	2.30 (1.97–3.71)	3.06 (1.43–4.27)	0.999	3.93 (3.39–5.64)	0.013
CS	2.85 (2.36–3.67)	3.15 (1.91–4.16)	0.923	4.07 (3.53–4.99)	0.016
LSPV	2.90 (2.18–3.10)	1.81 (1.58–3.52)	0.462	3.03 (1.96–3.72)	0.424
RSPV	2.78 (2.42–2.96)	2.12 (1.50–3.68)	0.624	2.81 (1.80–3.54)	0.894

Fe V, femoral vein; RA, right atrium; CS, coronary sinus; LSPV, left superior pulmonary vein; RSPV, right superior pulmonary vein.
Data are expressed as median values and interquartile ranges.
[a]Paroxysmal vs. control.
[b]Permanent vs. control.

levels in the femoral vein, right atrium, and coronary sinus were greater in patients with permanent AF than in controls (*Table 2* and *Figure 1*). However, no IL-8 differences were found in the samples from the pulmonary veins. Consequently, an IL-8 concentration gradient appeared in patients with permanent AF, with the levels in the femoral vein, right atrium, and coronary sinus greater than the levels in the pulmonary veins ($P = 0.023$, *Figure 1*). These findings remained unchanged when the data were re-analysed after removing the patient with hypertension from the paroxysmal AF group and the three patients with hypertension from the permanent AF group. In other words, the presence of hypertension did not have a major impact on the results of the present study.

A close correlation existed between the IL-8 levels in the femoral vein and right atrium (Spearman's rank correlation coefficient $R = 0.929$, $P = 0.014$), and between the IL-8 levels in the femoral vein and coronary sinus, respectively (Spearman's rank correlation coefficient $R = 0.976$, $P = 0.009$) (*Figure 2*). However, no significant correlation existed between the IL-8 levels at these locations and the IL-8 levels in the pulmonary veins.

Discussion

This report presents the results of the first clinical study that aimed at assessing the source of inflammation in patients with AF. The main findings are: (i) patients with paroxysmal AF and with no other concomitant heart and inflammatory conditions do not have elevated plasma levels of C-reactive protein, IL-6, and IL-8; (ii) patients with permanent AF and with no other concomitant heart and inflammatory conditions do not have elevated plasma levels of C-reactive protein and IL-6; however (iii) they do have elevated IL-8

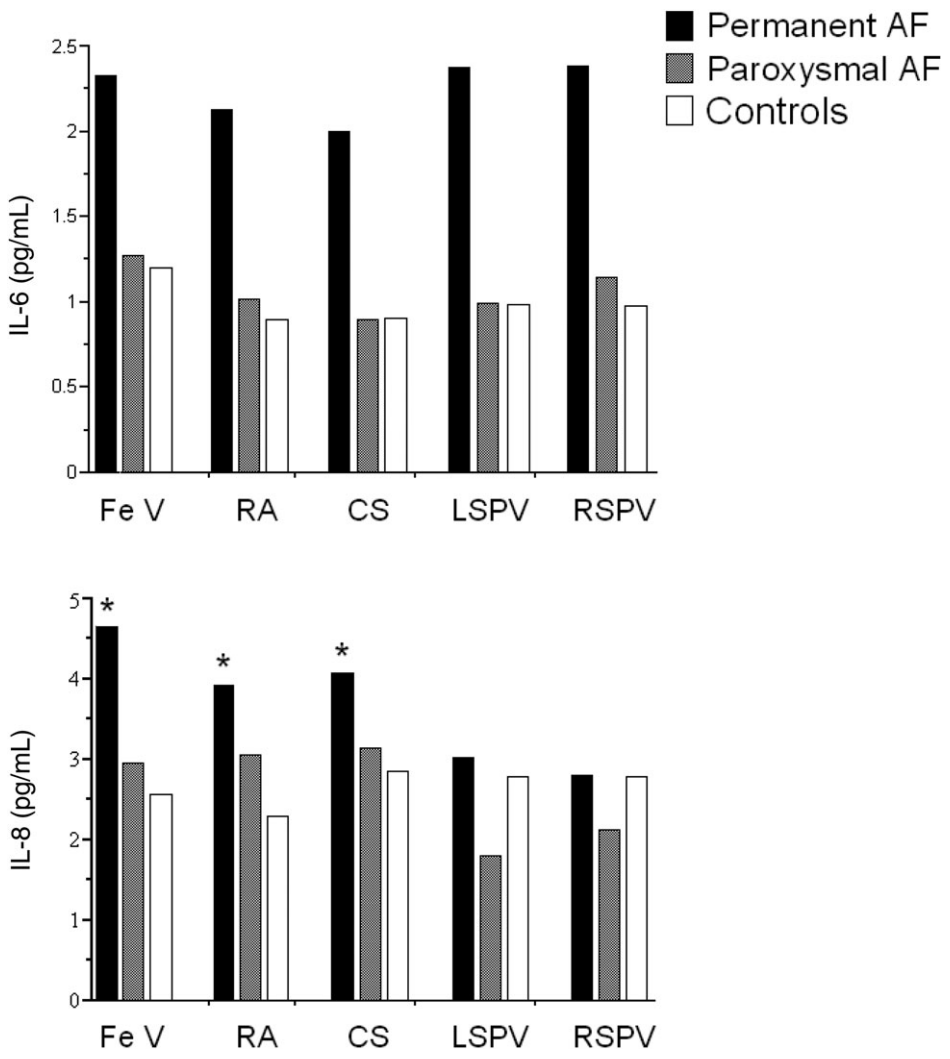

Figure 1 Median levels of interleukin-6 and -8 in the femoral vein (Fe V), right atrium (RA), coronary sinus (CS), left superior pulmonary vein (LSPV), and right superior pulmonary vein (RSPV). Asterisks indicate statistical significance. In patients with permanent atrial fibrillation, the plasma levels of interleukin-8 in the femoral vein, right atrium, and coronary sinus were greater than the interleukin-8 levels in the pulmonary veins ($P = 0.023$). No such gradient was found in controls or in patients with paroxysmal atrial fibrillation.

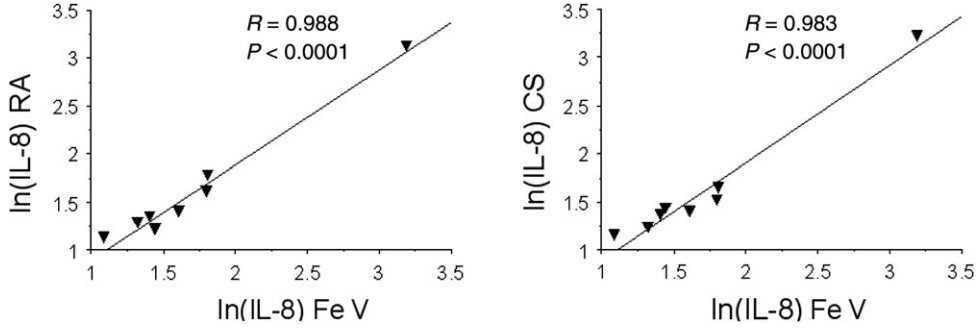

Figure 2 Regression plots showing very close correlation between interleukin-8 levels in the femoral vein (Fe V), right atrium (RA), and coronary sinus (CS). On the basis of the skewed distribution, the values had to be logarithmic-transformed before computing these plots. A similar high-degree correlation existed even for untransformed data, as revealed by the Spearman rank correlation coefficients.

levels in the systemic circulation and in the heart, but not in the pulmonary circulation.

The similar levels of inflammatory markers in patients with paroxysmal AF and controls were consistently noted at all sites sampled, irrespective of the rhythm during blood sampling (i.e. sinus rhythm or AF) or the duration of the history of AF. In other words, there was no evidence of any ongoing inflammatory reaction (at least as defined by the studied inflammatory markers) in this group of patients, neither in the heart nor in the systemic or the pulmonary circulation, neither in patients with sinus rhythm nor in those with AF at the moment of blood sampling. These findings

are consistent with those recently reported by Ellinor *et al*.[5] who found no differences in C-reactive protein levels between healthy controls and patients with idiopathic AF without hypertension. The same authors noted, however, elevated C-reactive protein levels in patients with idiopathic AF and with hypertension. Subsequent multivariate analysis indicated that this finding was attributable to increased body mass index in AF patients with hypertension when compared with controls. The body mass index did not differ significantly among our patient groups, which could provide an explanation to our results. Collectively, the present study and that of Ellinor *et al*. suggest that paroxysmal AF itself is not associated with elevated levels of C-reactive protein, IL-6, and IL-8 in the heart and in the systemic and pulmonary circulation. Moreover, in the present study, patients with permanent AF did not have elevated levels of C-reactive protein and IL-6. This finding is in concordance with those reported by Conway *et al*.[4] and Roldan *et al*.[20] in larger cohorts of patients with permanent AF, in which there were no evidence of raised levels of C-reactive protein and IL-6 after adjusting for associated co-morbidities. This indicates that permanent AF itself is not associated with elevated levels of C-reactive protein and IL-6. Taken together, these data seem to support the concept that the elevated levels of C-reactive protein and IL-6 in patients with AF reported in other studies[1–6] were likely related to the presence of other co-morbid conditions that existed in these patient cohorts rather to AF itself.

Interestingly, however, the patients with permanent AF had raised levels of IL-8 in the samples from the femoral vein, right atrium, and coronary sinus. A concentration gradient was noted, with higher IL-8 levels in the femoral vein, right atrium, and coronary sinus and lower levels in the pulmonary veins. Also, there was a high-degree correlation among the IL-8 levels from the femoral vein, right atrium, and coronary sinus. Along with the normal levels of C-reactive protein and IL-6, these findings suggest a low-grade inflammatory process originating mainly in the systemic circulation and not associated with an acute phase reaction. In addition, the elevated levels of IL-8 in patients with permanent AF but not in those with paroxysmal AF suggest a link between inflammation and long-lasting AF.

The source of IL-8 in these patients remains to be determined. This cytokine can be synthesized by various cell types, including monocytes, macrophages, hepatocytes, fibroblasts, and endothelial cells.[21] Several clinical studies have reported elevated biomarkers of vascular endothelial damage/dysfunction in patients with permanent AF.[22,23] Therefore, one could speculate that the vascular endothelium in the systemic circulation could have been a source of IL-8 in our patients. Although the presence of hypertension in some patients might have played a role in this process,[24] it is noteworthy that the elevated IL-8 levels in the samples from the femoral vein, the right atrium, and the coronary sinus remained significant even when re-analysing the data after removing the patients with hypertension. This fact suggests that it is unlikely that hypertension had a major impact on these findings. The exact mechanism underlying the process of endothelial damage/dysfunction remains, therefore, unclear.

It should be remarked that in parallel with the IL-8 production in the systemic circulation, a process of IL-8 consumption in the pulmonary circulation could have existed as well, as suggested by the concentration gradient between the right atrium and the pulmonary veins. It is unlikely that this gradient was due to a dilution by bronchial blood, as the bronchial arterial blood constitutes only 5% of the pulmonary venous return.[25] An IL-8 retention during pulmonary passage seems therefore more probable.

Regardless of the mechanism underlying the concentration pattern of IL-8, it could be speculated that the elevated levels of IL-8 in the right atrium and coronary sinus are associated with increased amounts of IL-8 in the cardiac tissue. Interleukin-8 is an important activator and a powerful chemoattractant for neutrophiles,[26] thereby promoting neutrophil-mediated organ injury.[27,28] Therefore, it could be assumed that a direct toxic effect of IL-8 on the atrial tissue might have played a role in the arrhythmia maintenance in patients with permanent AF in the present study. This hypothesis raises the question whether IL-8 lowering therapy might have an effect on the prevention of AF permanence in patients with paroxysmal AF.

Study limitations

Some limitations of our study should be noticed. First, the lack of significance in the levels of inflammatory markers in the present study may be related to the relatively small sample size. The results should therefore be interpreted with caution. Secondly, it could be argued that patients with WPW syndrome may not be the ideal reference group in such studies. These patients were selected as controls because the study design requires access to the left atrium and blood sampling from the pulmonary veins. However, unlike AF patients, WPW patients without AF have normal atrial and ventricular histology.[16] Thirdly, some patients with AF had hypertension, which might have affected the plasma levels of the inflammatory markers studied.[24] However, as detailed in the Results section, the findings of the present study remained unchanged when re-analysing the data after removing these patients, suggesting that it is unlikely that hypertension had a major impact on the levels of C-reactive protein, IL-6, and IL-8. Fourth, it could also be argued that the process of catheterization *per se* induced an artificial increase in the inflammatory markers that overwhelmed a possible low-level inflammatory state in AF patients. Indeed, studies both in healthy subjects and in patients with coronary artery disease showed that indwelling venous or arterial catheters may lead to local production of C-reactive protein, IL-6, and IL-8.[29–31] However, the increase in the plasma concentration of these inflammatory markers was detectable only after 3 h from the insertion of the catheters, whereas in our patients, blood sampling was performed well before this time point, usually within 45 min from the moment of the insertion of the first sheath. Finally, as some anti-arrhythmics may owe anti-inflammatory properties,[32] the level of inflammatory indexes in the present study may have been influenced by the fact that these drugs (as detailed in *Table 1*) were not discontinued prior to ablation in AF patients.

Conclusions

The present study supports the concept that patients with paroxysmal AF and no concomitant heart or inflammatory conditions do not have elevated levels of inflammatory

markers. However, patients with permanent AF and no concomitant heart or inflammatory conditions appear to have elevated IL-8 levels in the systemic circulation, the right atrium, and the coronary sinus, but not in the pulmonary veins. This finding, along with a high-degree correlation among IL-8 levels in the systemic circulation, right atrium, and coronary sinus, suggests an inflammatory reaction associated with long-lasting AF and originating mainly in the systemic circulation.

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Conflict of interest: none declared.

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