Inflammatory biomarkers in symptomatic atrial fibrillation: a case-control study

A. Jackson[1], O. Frobert[1], D. Boye Larsen[2], R. Giordano[2], L. Arendt-Nielsen[2], A. Bjorkenheim[1]

[1]Orebro University Hospital, Orebro, Sweden
[2]Aalborg University, Aalborg, Denmark

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Background: Atrial fibrillation (AF) is associated with significant morbidity and healthcare burden. While some patients remain asymptomatic, others experience debilitating symptoms. Traditional factors such as heart rate and rhythm irregularity do not fully explain this variability, suggesting that additional mechanisms, including inflammation, contribute to symptom severity.

Purpose: We aimed to investigate inflammation-associated protein profiles in patients with symptomatic AF before and after ablation compared to controls.

Methods: This case-control study included 100 patients aged 18–75 years with symptomatic paroxysmal or persistent AF scheduled for a first catheter ablation (pulmonary vein isolation) and 100 age- and sex-matched controls without AF. Symptom burden was assessed using the AF6 questionnaire (score range 0-60) and the modified European Heart Rhythm Association (EHRA) symptom scale. Peripheral blood samples were collected from AF patients both before and the day after ablation, and once from controls. Proteomic profiling was performed using the Olink Target 96 Inflammation panel. In addition, six AF-related proteins—Cystatin C, N-terminal pro B-type natriuretic peptide (NT-proBNP), high-sensitivity (hs) C-reactive protein (CRP), cancer antigen 125 (CA-125), hs troponin, and S100-calcium binding protein B (S100B)—were analysed separately. Principal component analysis and linear regression models (adjusted for baseline value, age, sex, rhythm at admission, baseline creatinine, and baseline NT-proBNP) were used to examine biomarker profiles, with significance defined as $p<0.05$ after Bonferroni correction.

Results: The median AF6 sum score was 23 (IQR: 14-32), and most patients were classified as EHRA III, indicating severe symptoms before ablation. Fifty-two inflammatory biomarkers, including interleukin-6, fibroblast growth factor-21, and interleukin-10 were significantly increased after compared to before ablation. Principal component analysis showed partial separation between AF patients (both pre- and post-ablation) and controls, indicating distinct inflammatory profiles, with some overlap between pre- and post-ablation (Figure 1). Among the six targeted proteins, all were elevated except S100B. In the case-control comparison, 12 biomarkers were significantly increased in AF patients, and NT-proBNP and Cystatin C were elevated in the separate analysis. Twenty-three patients experienced at least one ECG-verified AF recurrence between the end of the three-month blanking period and the six-month follow-up.

Conclusion: Our findings indicate that symptomatic AF is associated with a distinct inflammatory biomarker signature that is further modified by catheter ablation. These results highlight an acute inflammatory response and potential immune modulation post-ablation, underscoring the potential of inflammatory biomarkers in refining personalised management strategies for patients with symptomatic AF.

Table 1. Baseline characteristics

	N	Controls	AF
		$N = 100$	$N = 99$
Age	199	51.75 61.00 69.00	55.50 62.00 69.00
Sex : Female	199	30% (30)	29% (29)
Male		70% (70)	71% (70)
BMI	199	23.73 25.16 27.23	25.06 27.17 30.61
Smoking : No	199	77% (77)	65% (64)
Smoker or previous smoker		23% (23)	35% (35)
Rythm at admission : AF	199	0% (0)	14% (14)
SR		100% (100)	86% (85)
Alcohol : Moderate to high use	199	13% (13)	13% (13)
No or low use		87% (87)	87% (86)
Hypertension : No	199	77% (77)	54% (53)
Yes		23% (23)	46% (46)
Heart failure : No	199	100% (100)	92% (91)
Yes		0% (0)	8% (8)
History of Stroke or TIA : No	199	98% (98)	99% (98)
Yes		2% (2)	1% (1)
Obstructive sleep apnoea : No	199	92% (92)	93% (92)
Yes		8% (8)	7% (7)
Kidney disease : No	199	100% (100)	100% (99)
Yes		0% (0)	0% (0)
Antiarrhythmic therapy : No	199	100% (100)	38% (38)
Yes		0% (0)	62% (61)
Beta-blockers : No	199	95% (95)	26% (26)
Yes		5% (5)	74% (73)
ARB or ACE inhibitor : No	199	84% (84)	54% (53)
Yes		16% (16)	46% (46)
Verapamil or diltiazem : No	199	90% (90)	82% (81)
Yes		10% (10)	18% (18)
Duration of AF [years]	99		2 4 9
AF6 sum score	199	0 0 0	14 23 32
EHRA class : EHRA IIa	199	0% (0)	9% (9)
EHRA IIb		0% (0)	44% (44)
EHRA III		0% (0)	45% (45)
EHRA IV		0% (0)	1% (1)

$_a\,b\,c$ represent the lower quartile a, the median b, and the upper quartile c for continuous variables.
N is the number of non–missing values. Numbers after percents are frequencies.
The categories EHRA IIa, IIb, III and IV represent mild, moderate, severe, and disabling symptoms from atrial fibrillation, respectively.
AF; atrial fibrillation, BMI; body mass index, SR; sinus rhythm, TIA; transient ischaemic attack, ARB; angiotensin receptor blockers, ACE; angiotensin converting enzyme, AF6; atrial fibrillation 6 symptom questionnaire, EHRA; European Heart Rhythm Association.

Table 1. Baseline characteristics

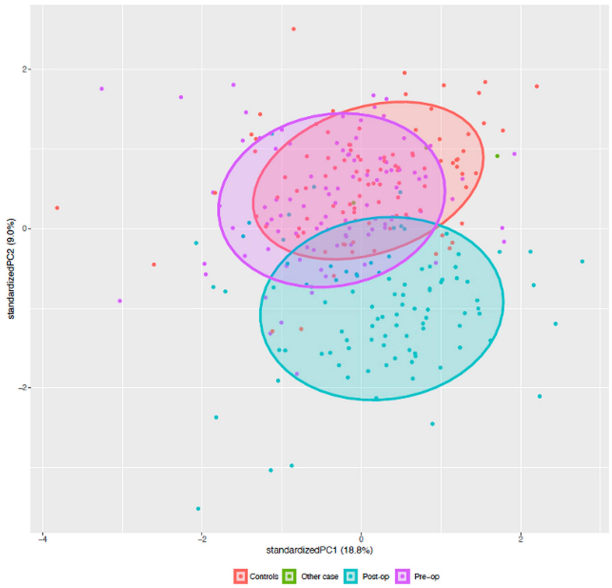

Figure 1. Principal component analysis of inflammatory biomarker profiles in subjects with symptomatic atrial fibrillation before (pre-op) and after (post-op) catheter ablation, compared to controls without atrial fibrillation. Each point represents an individual participant, and the ellipses indicate the 68% confidence region for each group.

Figure 1. Principal component analysis