

Research article

# Inflammation and fibrosis in patients with atrial fibrillation and heart failure: is there a need for rehabilitation?

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**Abstract:** Background: Atrial fibrillation (AF) is increasingly prevalent among the general population as well as in those exhibiting heart failure (HF), and the symptomatology progressively worsens when both conditions are met. The aim of this study was to analyse the role of inflammation and fibrosis biomarkers in patients with AF and HF.

**Methods:** 108 subjects with heart failure were enrolled in the study. All patients were evaluated clinically, biologically and echocardiographically. Plasma values of NT-proBNP, Gal-3 and sST2 were determined.

**Results:** Out of all patients, 64.8% experienced at least one AF event. There were no differences in the mean left ventricular ejection fraction between the groups, which was  $39.4 \pm 11.2\%$ . In terms of left atrium dimensions, the values in the AF group were significantly higher ( $51.19 \pm 7.3$  vs.  $44.68 \pm 7.16$  mm,  $p < 0.001$ ). AF history was associated with a trend of decreased eGFR -  $59,22 \pm 24,1$  ml/min/1.73m<sup>3</sup> vs  $75,95 \pm 29,1$  ml/min/1.73m<sup>3</sup> ( $p = 0.006$ ). There was no statistically significant difference in the level of HF biomarkers (sST2, Galectin-3 and NT-pro BNP) between individuals with or without AF.

**Conclusion:** Patients with HF are at greater risk to develop AF. HF biomarkers (sST2, Galectin-3 and NT-pro BNP) are not influenced by the presence of AF.

**Keywords:** Atrial fibrillation, inflammation biomarkers, cardiac rehabilitation.

## 1. Introduction

The role of heart failure (HF) biomarkers (Galectin-3, NT-proBNP and sST2) is still uncertain in patients with heart failure and atrial fibrillation (FA), both diseases indirectly influencing their value. If regarding NT-proBNP current guidelines recommend its routine dosing in heart failure patients, data regarding Galectin-3 and sST2 are scarcer. American guidelines comprise some recommendations regarding Gal-3, both in terms of risk stratification and evaluation of prognosis for patients with HF [1, 2]. Galectin-3, NT-proBNP and sST2 are involved in the pathophysiological mechanisms of inflammation and fibrosis in HF [3, 4]. At the same time, there is emerging literature data that advocates

for the involvement of these biomarkers in atrial fibrosis that is a substrate for AF [5, 6]. In order to improve their prognosis, patients with HF and AF should be included in comprehensive cardiovascular rehabilitation programs. It would be interesting to determine if long-term physical training programs have an impact on the level of these biomarkers, which would argue for its role in the reverse atrial and ventricular remodelling.

The aim of this study was to analyse the main determinants of atrial fibrillation in patient with heart failure, as it is important to evaluate these patients as carefully as possible, considering the multifactorial etiology of atrial fibrillation and treatment peculiarities.

## 2. Results

The baseline characteristics of the patients are summarized in table I. Out of the 108 patients, 60.2% were men, 64.8% had at least one episode of AF, and 48.15% were known to have diabetes. AF was present in 61.5% of diabetic patients compared to 67.9% of those without diabetes ( $p = 0.49$ ). Analyzing table I, we found that in univariate analysis, there were no significant differences between patients with AF vs. those without AF regarding age, BMI or left ventricular ejection fraction (LVEF) ( $p=NS$ ). The risk of women with DM for developing AF was higher (OR 1.21), but it failed to reach statistical significance in our study group ( $p=0.685$ ). There was a significant difference regarding AS size between patients with AF and those without ( $p<0.001$ ). Also, the degree of renal insufficiency was significantly higher among patients with atrial fibrillation compared to those without (creatinine –  $p = 0.011$ , creatinine clearance –  $p=0.006$ ). Regarding the lipid profile, it was not influenced by the presence of atrial fibrillation. Body mass index (BMI) was similar between diabetic ( $30.2 \pm 5.6$  kg/m<sup>2</sup>) and non-diabetic ( $28.5 \pm 6.4$  kg/m<sup>2</sup>) subjects (table I).

**Table 1.** Main parameters according to atrial fibrillation

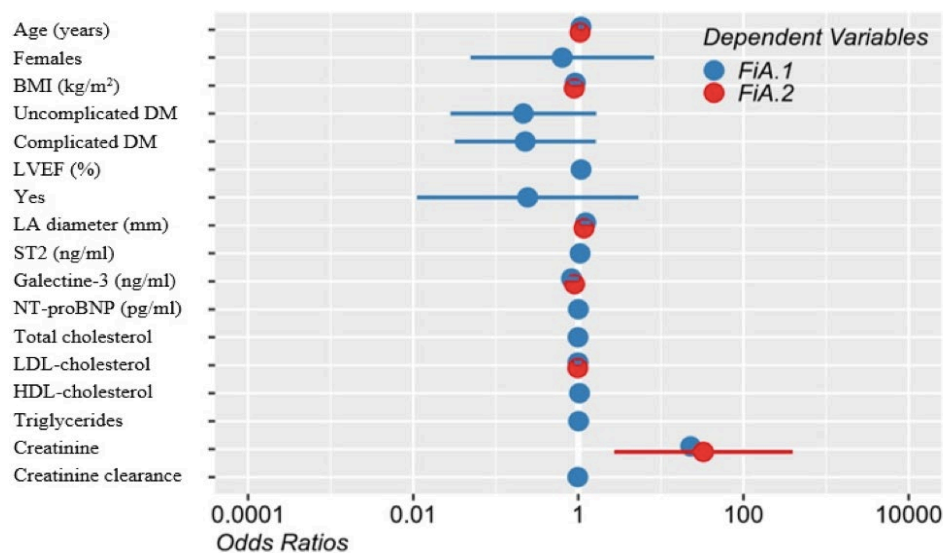
Variable	All patients	Atrial fibrillation	Sinus rhythm	p-value
Age, years (mean $\pm$ SD)	70.31 $\pm$ 9.6	71.23 $\pm$ 9.81	68.63 $\pm$ 9.13	0.129
Female gender, (n%)	43 (39.8%)	29 (41.4%)	14 (36.8%)	0.685
BMI, kg/m <sup>2</sup> (mean $\pm$ SD)	29.27 $\pm$ 6.0	29.25 $\pm$ 6.34	29.30 $\pm$ 5.43	0.853
Diabetes, (n%)	55 (50.92%)	32 (58.18%)	20 (36.36%)	0.525
Total cholesterol, mg/dl (mean $\pm$ SD)	161.46 $\pm$ 48.2	155.29 $\pm$ 46.9	173.14 $\pm$ 49.1	0.104
LDL- cholesterol, mg/dl (mean $\pm$ SD)	96.43 $\pm$ 38.8	92.77 $\pm$ 38.2	103.35 $\pm$ 39.5	0.245
HDL-cholesterol, mg/dl (mean $\pm$ SD)	41.15 $\pm$ 18.4	39.10 $\pm$ 12.9	45.03 $\pm$ 25.5	0.359
Triglycerides, mg/dl (mean $\pm$ SD)	124.26 $\pm$ 65.9	124.33 $\pm$ 73.2	124.14 $\pm$ 50.0	0.283
Creatinine, mg/dl (mean $\pm$ SD)	1.24 $\pm$ 0.567	1.34 $\pm$ 0.64	1.04 $\pm$ 0.319	0.011
Clearance Cr (mean $\pm$ SD)	65.01 $\pm$ 27,0	59.22 $\pm$ 24.1	75.95 $\pm$ 29.1	0.006
LVEF, % (mean $\pm$ SD)	39.48 $\pm$ 11.2	39.60 $\pm$ 10.7	39.26 $\pm$ 12.2	0.884
LVEF > 50%, n (%)	12 (11.1%)	7 (10,0%)	5 (13.2%)	0.750
Left atrium, mm (mean $\pm$ SD)	48.86 $\pm$ 7.86	51.19 $\pm$ 7.3	44.68 $\pm$ 7.16	< 0.001
ST2, ng/ml (mean $\pm$ SD)	44.19 $\pm$ 24.3	46.94 $\pm$ 26.3	38.89 $\pm$ 19.4	0.196
Galectin-3, ng/ml (mean $\pm$ SD)	14.22 $\pm$ 5.33	14.28 $\pm$ 5.48	14.11 $\pm$ 5.12	0.984
NT-proBNP, pg/ml (mean $\pm$ SD)	3410.86 $\pm$ 3979.3	3684.40 $\pm$ 4476.1	2930.32 $\pm$ 2904.2	0.482

N (%) or mean (standard deviation), p – Fisher Chi<sup>2</sup> test or Mann-Whitney test;  $\mu \pm$  SD = mean  $\pm$  standard deviation; OR/RR = odds-ratio / relative risk (with 95% CI) and p

calculated by the Fisher test); V = Cramer V (p calculated by the Chi<sup>2</sup> test); BMI = body mass index; LVEF = left ventricular ejection fraction

Regarding the cardiovascular risk factors there weren't significant differences between patients with and without AF (figure 1). There was a higher risk of developing atrial fibrillation in patients with elevated serum creatinine levels (figure 1).

**Figure 1.** Illustration of the hazard rate for each studied parameter



The mean value of LVEF was 36.4±11.3%, with no significant difference between patients with AF vs those without (39.60±10.7 vs 39.26±12.2) (table I).

Regarding the dimensions of the left atrium, determined on echocardiography, there were significant differences between patients with and without AF compared to the whole cohort.

Subjects with a history of AF had a tendency for higher baseline creatinine levels and consequently lower clearance—51.1±23.9 ml/min/1.73m<sup>3</sup> compared to 75.9±29.1 ml/min/1.73 m<sup>3</sup> (p=0.0015).

Among patients with DM, there was no significant difference in glycemic control as a determining factor for the development of atrial fibrillation (130.4±52.2 mg/dl in the group of those with FiA vs 129.4 ± 41.9 mg /dl in the non-AF, p=NS).

Regarding the value of heart failure specific biomarkers, we obtained the following results. The mean value of sST2 was 44.19±24.3 ng/ml: 46.9±19 ng/ml in patients with AF compared to 38.89 ng/ml in those without AF (p=0.196). The mean value of galectin-3 was 14.22±5.33 pg/ml: 14.28±5.48 pg/ml vs 14.11±5.1 pg/ml (p=0.984). The mean value of NT-proBNP was 3684.4 pg/ml in patients with AF compared to 2930.32 pg/ml in those without AF (p=0.482) (table I).

### 3. Discussion

In the present study, 108 patients with decompensated HF, NYHA classes II-IV, were included, of which 70 (64.8%) presented at least one episode of atrial fibrillation. Previous studies showed that the prevalence of AF increases with the severity of heart failure [7]. Patients with HF functional class NYHA II have a prevalence of AF of 5% in the SOLVED study, while the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) recorded a prevalence of approximately 50% in patients with atrial fibrillation and HF functional class NYHA IV [8,9].

In our study, the risk of women with DM to develop AF was higher (OR 1.21), but not statistically significant (p = 0.685). Multiple previous studies have shown that women generally have a lower age-adjusted incidence of atrial fibrillation compared to men;

however, given the greater longevity of women, the absolute numbers of men and women with AF are similar [10].

The mean left ventricular ejection fraction was  $39.48 \pm 11.2\%$ , with no significant differences between patients with AF and those without.

Increased NT-proBNP values were recorded in all groups, with mean values of  $3410.86 \pm 3979.3$  pg/ml, well above the cut-off value of 125 pg/ml indicated in the ESC guideline of IC [1,7].

NT-proBNP is an important biomarker that is part of the usual diagnosis workup of HF, but it is also a strong predictor of prognosis in these patients [1,7].

In heart failure subjects, NT-proBNP levels are influenced by the presence of concomitant atrial fibrillation, making it difficult to distinguish between HF and AF in patients with elevated NT-proBNP [11,12].

The diagnosis of HF, especially with preserved LVEF, in patients with AF remains challenging, as signs and symptoms, echocardiographic abnormalities, and elevated NT-proBNP levels can be caused by AF alone or by a combination of AF and HF [13].

In our study, there were no significant differences between NT-proBNP values in patients with or without atrial fibrillation.

Recent studies demonstrate that patients in sinus rhythm with a history of paroxysmal AF have significantly lower NT-proBNP levels, similar to AF-free patients, and in contrast to subjects with permanent AF [14]. Another study that included elderly patients with HF and AF, significantly higher values of this biomarker were recorded only in the presence of diabetes mellitus [15].

This finding could explain the absence of a significant difference in NT-proBNP values in the present study, as there was no separate analysis according to the type of AF.

Regarding other studied biomarkers, sST2 and Gal-3, they were not statistically different between patients with or without AF.

Serum Gal-3 level has been approved as a diagnostic marker for risk stratification and prognostic assessment in patients with HF according to the ACC/AHA/HFSA Guidelines for the Management of HF [2]. Thus, Gal-3 can play an important role in assessing the risk of hospitalization and cardiovascular death [16]. In the HF-ACTION study, increased levels of Gal-3 and NT-pro BNP were correlated with an increased the risk of hospitalizations for heart failure [17]. Regarding atrial fibrillation, Gal-3 is probably linked to atrial fibrosis through multiple mechanisms. In a recent study, in the presence of AF, higher Gal-3 was associated with renal dysfunction, female sex and a history of gout [18].

Multiple studies have demonstrated the correlation between Gal-3 and worsening kidney function, being a marker of negative prognosis in patients with diabetes and heart failure. However, its values did not directly correlate with the LVEF [19,20]. Multiple papers propose the use of Gal-3 as a prognostic marker in diabetic nephropathy, as it displays significantly higher levels in patients with kidney damage [21,22]. It seems to be a good prognostic marker when it comes to the need for dialysis in these patients [21,22].

The role of sST2 in heart failure is very much debated. Together with NT-pro-BNP, it would represent an important marker for diagnosing heart failure with preserved ejection fraction, but also for treatment monitoring [23]. The present study recorded an average value of sST2 of  $44.19 \pm 24.3$  ng/ml and higher values of sST2 were recorded in patients with a history of atrial fibrillation, but without reaching statistical significance. At the same time, because it is also a marker of myocardial fibrosis, the ST2 value are increased in patients with AF [24,25]. A Chinese study demonstrated that sST2 levels were an independent factor associated with the presence of AF in patients with heart failure. This suggests the need for optimization of treatment strategies in patients with heart failure and AF [26].

At the same time, there are studies that make a strong point for the involvement of sST2 in the presence of atrial fibrosis in AF [27].

When it comes to both Gal-3 and sST2 as markers of fibrosis, we would like to emphasize the fact that recent research indicate a possible direct relationship between elevated levels of sST2 and Gal-3 and three gene polymorphisms in patients with AF (rs2274273 and galectin -3 levels and rs1558648 and sST2 levels) [28].

Our study demonstrated a significant increase in the degree of renal damage in patients with a history of AF. They presented significantly higher levels of serum creatinine and lower values of creatinine clearance. Atrial fibrillation and chronic kidney disease (CKD) have common risk factors, such as hypertension, obesity, diabetes, so the two conditions often coexist [29,30]. Up to 20% of patients with CKD have symptomatic AF, while around 50% of patients with AF present with some degree of renal failure [31,32].

Finally, we would like to emphasize the fact that after initial HF stabilization and thorough AF rhythm or rate control, these patients must be included in specific cardiac rehabilitation programs. It would be important to evaluate the level of these biomarkers in the long term follow up after physical training programs, to see if there is indeed a notable decrease [33]. A study published in 2017 showed that physical training programs in HF patients with reduced ejection fraction caused a significant decrease in the levels of Galectin-3, MR-proADM, sST2 and MR-proANP [34].

In conclusion, the presence of atrial fibrillation did not significantly influence the values of certain specific HF biomarkers, larger studies being needed in order to clarify this finding.

#### 4. Materials and Methods

108 subjects with decompensated heart failure (NYHA class II-IV) were enrolled, with a mean age of 70.3±9.6 years, 60.2% men, 64.8% with atrial fibrillation. All patients were evaluated clinically, biologically and echocardiography was performed. Patients were admitted to the Cardiology Department of the Rehabilitation Hospital Cluj-Napoca. Heart failure criteria were defined according to the current guidelines published by the European Society of Cardiology.

The plasma value of NT-proBNP was determined from heparinized venous blood, using Roche Cardiac Reader kits, which allow the detection of a concentration of NT-proBNP between 60 and 3000 pg/ml.

Samples were collected from all subjects on the first day of admission, a value of NT-proBNP above 125 pg/ml was considered suggestive for the diagnosis of heart failure, according to the recommendations of the current ESC guidelines [1,7].

Serum Galectin was determined using ELISA kits for the quantitative evaluation of human Galectin-3 in plasma, a measurement based on the standard sandwich method of binding the enzyme to an immuno-sorbent. A monoclonal antibody to Galectin-3 was pre-coated on 96 plates with the standards and test samples included. Subsequently, a biotinylated goat polyclonal antibody highly specific for Galectin-3 was added. After a determined period of incubation, washing was performed with PBS buffer, later the avidin-biotin-peroxidase complex was added, and the unbound conjugates were washed using the buffer. HRP-TMB substrate was used to visualize the enzymatic reaction in the blue color spectrum. The stop solution was then added to the plate, producing a yellow coloration. The intensity of the staining was in direct correlation with the concentration of human Galectin-3 of the samples, the detection range being between 10 and 100 ng/ml.

ST2 was also quantified by a high-sensitivity sandwich monoclonal assay. The antibodies used were obtained from a recombinant protein based on the human cDNA clone of the soluble ST2 sequence. The detection limits for ST2 was between 2 and 200 ng/ml.

The selected patients were informed about the study protocol and gave their signed informed consent. The study was carried out in agreement with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

The patients were divided into two groups-with and without atrial fibrillation.

Statistical analysis. A database was created using spreadsheets, statistical analysis being processed using version 3.6.1 of the R software for Linux. A p value less than 0.05 was considered statistically significant. Means  $\pm$  standard deviation and median (for extreme values) were used to describe numerical variables, as well as frequency for qualitative variables. Depending on the distribution of the data, either parametric t tests, ANOVA or non-parametric alternative tests (Mann-Whitney, Kruskal-Wallis test) were used to evaluate the differences in numerical variables. Chi-square test with Cramer V coefficients was used for qualitative variables. Post-hoc analysis was performed using the paired Mann-Whitney test. Correlations were assessed using Spearman rho coefficients, and serum NT-proBNP values were log-normally distributed, with transformation prior to hypothesis testing.

## 5. Conclusions

In conclusion, the presence of atrial fibrillation did not significantly influence the values of certain specific HF biomarkers, larger studies being needed in order to clarify this finding.

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**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

**Data Availability Statement:** The data can be provided on reasonable request from the corresponding author.

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