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# Galectin-3 in patients undergoing ablation of atrial fibrillation

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ABSTRACT

*Background:* Mechanisms of maintenance of atrial fibrillation are known to include fibrosis. Galectin-3, as a biomarker of fibrosis, may be a valuable marker of atrial remodeling. We sought to find whether there was a link between clinical features and higher galectin-3 levels in patients with atrial fibrillation.
*Methods:* Serum concentrations of Galectin-3 were determined in a consecutive series of patients addressed for ablation of atrial fibrillation.
*Results:* One-hundred-and-eighty-seven patients were included, 56% having a paroxysmal type of atrial fibrillation. Mean Galectin-3 concentration was 14.5 ± 5.5 ng/mL. Age, persistent form of atrial fibrillation, underlying cardiac disease, heart failure, decreased left ventricular ejection fraction (LVEF), hypertension, diabetes, treatment with ACEI/ARB, enlarged left atrium and renal insufficiency were associated with higher Galectin-3 levels. Importantly, persistent form of atrial fibrillation, female sex, and LVEF <45% were independent predictors (OR 13.9, p = 0.01, OR = 11.7, p = 0.03, and OR 54.2, p = 0.04, respectively) of higher Galectin-3 levels (≥15 ng/mL).
*Conclusions:* Persistent type of atrial fibrillation is an independent predictor of higher Galectin-3 concentration. This biomarker of fibrosis may be implied in the mechanisms of atrial remodeling and maintenance of atrial fibrillation, and thus be helpful for the design of therapeutic strategy in patients with atrial fibrillation.


## 1. Introduction

Atrial fibrillation, characterized by rapid and irregular electrical activity within the atria, is associated with an increased risk of thromboembolic events, hospitalizations for heart failure, and overall mortality [1]. The natural history of the disease has several presentations and evolutions. Primary AF typically begins with paroxysmal episodes of arrhythmia, which by arbitrary definition last less than seven days and self-terminate spontaneously. It then may evolve towards so-called persistent AF, defined by more prolonged episodes lasting more than seven days and/or necessitating pharmacological or electrical cardioversion. AF with over than one year of continuous arrhythmia defines long-lasting or long-term persistent AF. Finally, the term permanent should be used whenever treatment refractory persistent AF is observed [2].

Patients may evolve very differently. Some patients will present persistent AF as a first manifestation of the disease, while some will pass through several years of paroxysmal episodes. Although the mechanisms involved in the evolution of the disease remain unclear, AF has been shown to lead to electrical remodeling and progressive fibrosis of the atria, which in turn favor AF perpetuation and chronicization: "AF begets AF" [3,4].

Evaluation of the fibrosis extent is thus important in order to assess the prognosis of the disease, and may be useful for choosing the most adapted therapeutic strategy. Indeed, strategies for AF ablation may differ according to the amount of diseased tissue, from a simple isolation of the pulmonary veins to an extensive ablation of both atria [5]. The specific efficacy of the different strategies also differs significantly, with extensive atrial fibrosis being associated to a poorer outcome after ablation of AF [6]. Accordingly, it has been proposed to use some antifibrotic agents in patients with AF [7,8].

Since the atrial wall is thin, evaluation of fibrosis within the atria remains difficult. While some authors have proposed to perform MRI, this technique could be difficult to access routinely [9].

Galectin-3 (Gal-3) is a member of the ß-galactoside-binding lectins family. Gal-3 has a pleiotropic distribution and could be found in the cytoplasm, in the nucleus and at the cell membrane or as a pentameric circulating form [3]. Gal-3 is highly expressed in fibrotic tissues, and

*Abbreviations:* AF, atrial fibrillation; MRI, magnetic resonance imaging; LVEF, left ventricular ejection fraction; BNP, brain natriuretic peptide; HF, heart failure; BMI, body mass index; LA, left atrium; TIA, transient ischemic attack; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; GFR, glomerular filtration rate.

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**Table 1**
Baseline characteristics for all patients.

| | TOTAL (N = 187) |
|---|---|
| Male (%) | 127 (68) |
| Age (years) | 62 ± 10 |
| BMI (kg/m$^2$) | 29 ± 6 |
| Paroxysmal AF (%) | 105 (56) |
| Lone AF (%) | 62 (33) |
| Structural Heart Disease | 46 (25) |
| Heart Failure (%) | 45 (24) |
| Hypertension (%) | 94 (50) |
| Diabetes Mellitus (%) | 34 (18) |
| TIA or Stroke (%) | 7 (4) |
| Vascular Atherosclerosis (%) | 16 (9) |
| $CHADS_2$ Score | 1.43 ± 1.15 |
| $CHA_2DS_2$_VASC Score | 1.90 ± 1.47 |
| ACE/ARB N (%) | 36 (19) |
| Betablocker N (%) | 62 (56) |
| Antiarrhythmic Drugs Class I/III N (%) * | 106 (57)/144 (77) |
| LA Diameter (mm) | 42 ± 7 |
| Index LA Volume (mL/m$^2$) | 66 ± 19 |
| LVEF (%) | 54 ± 11 |
| MDRD GFR (mL/min/1.73 m$^2$) | 74 ± 20 |
| hs-CRP (mg/L) | 5.0 ± 8.5 |
| BNP (ng/L) | 156 ± 253 |
| Galectin-3 (ng/mL) | 14.5 ± 5.5 |
| QRS width (ms) | 96 ± 20 |
| Sinus rhythm at admission (%) | 109 (58) |

* Antiarrhythmic drugs (≥1) prescribed before ablation.

upregulated in chronic inflammatory and fibrotic conditions in human [10–12]. It is mainly produced by activated macrophages, mast cells and eosinophils, and plays a role in cell adhesion and proliferation, increasing fibrosis. However, the respective mechanisms by which Gal-3 exerts fibrogenic activity are not completely depicted. Extracellular pentameric Gal-3 interaction with profibrotic effectors such as TGF-β1 could be a part of the pathway that initiates fibrogenesis. Gal-3 has a pivotal role in cardiac fibrosis [12]. Mammalian models of cardiac fibrosis demonstrate high level of Gal-3. Accordingly, it has been shown that Gal-3 inhibition prevents cardiac fibrosis [13].

Recently, Gal-3 has been suspected to play a role in promoting fibrosis within atria in patients with AF [3]. Gal-3 levels correlate with risk factors of cardiovascular disease such as hypertension, diabetes or obesity, and were shown elevated in heart failure [14]. For these patients, Gal-3 has been proposed as a biomarker to estimate their prognosis [15].

We thus hypothesized that a high level of Gal-3 could be primarily observed in patients with a persistent form of AF, who are prone to more extensive atrial fibrosis.

## 2. Materials and Methods

### 2.1. Inclusion

Consecutive patients with symptomatic AF referred to our department for ablation during the year 2013 were included in this study. Exclusion criteria included all non-cardiac conditions with expected elevated Gal-3 levels, such as liver cirrhosis, pancreatitis or chronic inflammatory disease. Patients with a history of ablation procedure for AF were also excluded. Collected clinical data included symptoms (EHRA classification) and history of arrhythmia, presence of thromboembolic risk factors (according to $CHADS_2$ and $CHA_2DS_2$-VaSC scores), and past and current medications. Trans-thoracic echocardiography and cardiac magnetic resonance imaging were performed to assess left ventricular function and left atrial diameter and volume.

The local ethics committee for human research approved the study protocol. All patients signed informed consent before inclusion.

### 2.2. Galectin-3

During the early stage of AF ablation procedure, blood samples were collected through the femoral vein sheath in order to determine the anticoagulation time. Dosage of serum level of Gal-3 was performed on the residual sample.

Determination of Gal-3 level was prospectively completed using the VIDAS Galectin-3 kit (bioMérieux, Marcy-l'Etoile, France). VIDAS Galectin-3 is an automated quantitative test. The kit measuring range is 3.3-100 ng/mL. The assay principle is a one-step immunoassay sandwich method with final fluorescent detection.

### 2.3. Statistical analyses

Analyses were performed using JMP version 9 (SAS Institute Inc., Cary, NC, USA). Numeric data were expressed as mean ± standard deviation (95% confidence interval). Student T-test and Chi-2 were performed for comparison between groups. A nominal logistic regression model was used to assess the factors independently associated with significantly higher Gal-3 levels (above the mean value). Main confounding factors were tested in univariate analysis, and parameters associated with elevated Gal-3 levels ($p < 0.10$) were used for analyses in the multivariate model. A p-value $<0.05$ was considered significant.

## 3. Results

### 3.1. Population

One-hundred-and-eighty-seven patients met the criteria for inclusion in the study. Patients were predominantly men with a mean age

**Table 2**
Characteristics of patients according to quartiles of Galectin-3 (ng/mL).

| | Q1 < 10.8 | Q2 10.8-13.4 | Q3 13.5-17.3 | Q4 > 17.3 | p |
|---|---|---|---|---|---|
| Galectin-3 (ng/mL) | 8.9 ± 1.2 | 12.0 ± 0.7 | 15.1 ± 1.1 | 21.9 ± 4.8 | <**0.0001** |
| Male Gender (%) | 79 | 79 | 60 | 64 | 0.12 |
| Age (years) | 58 ± 11 | 62 ± 8 | 64 ± 9 | 66 ± 10 | **0.004** |
| BMI (kg/m$^2$) | 26 ± 3 | 29 ± 6 | 31 ± 7 | 29 ± 6 | **0.03** |
| Paroxysmal AF (%) | 79 | 55 | 47 | 43 | **0.002** |
| Structural Heart Disease (%) | 19 | 19 | 21 | 38 | 0.13 |
| Heart Failure (%) | 9 | 12 | 26 | 50 | <**0.0001** |
| Hypertension (%) | 33 | 50 | 56 | 62 | **0.04** |
| Diabetes Mellitus (%) | 5 | 14 | 26 | 26 | **0.01** |
| LA Diameter (mm) | 40 ± 7 | 40 ± 6 | 45 ± 9 | 43 ± 7 | **0.006** |
| Index LA Volume (ml/m$^2$) | 62 ± 21 | 61 ± 15 | 69 ± 18 | 72 ± 19 | **0.04** |
| LVEF (%) | 57 ± 9 | 57 ± 8 | 52 ± 12 | 49 ± 12 | **0.005** |
| MDRD GFR (ml/min/1.73 m$^2$) | 81 ± 17 | 80 ± 23 | 75 ± 16 | 64 ± 20 | **0.0001** |
| hs-CRP (mg/L) | 4.4 ± 7.3 | 3.3 ± 3.9 | 4.1 ± 3.5 | 8.5 ± 14.1 | **0.01** |
| BNP (ng/L) | 86 ± 111 | 103 ± 194 | 214 ± 278 | 245 ± 368 | **0.0005** |