

# Inflammatory and Imaging-based Predictors of Atrial Fibrillation Recurrence after Pulmonary Vein Isolation Using Electroanatomical Mapping – the INFLAMAP Study

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## ABSTRACT

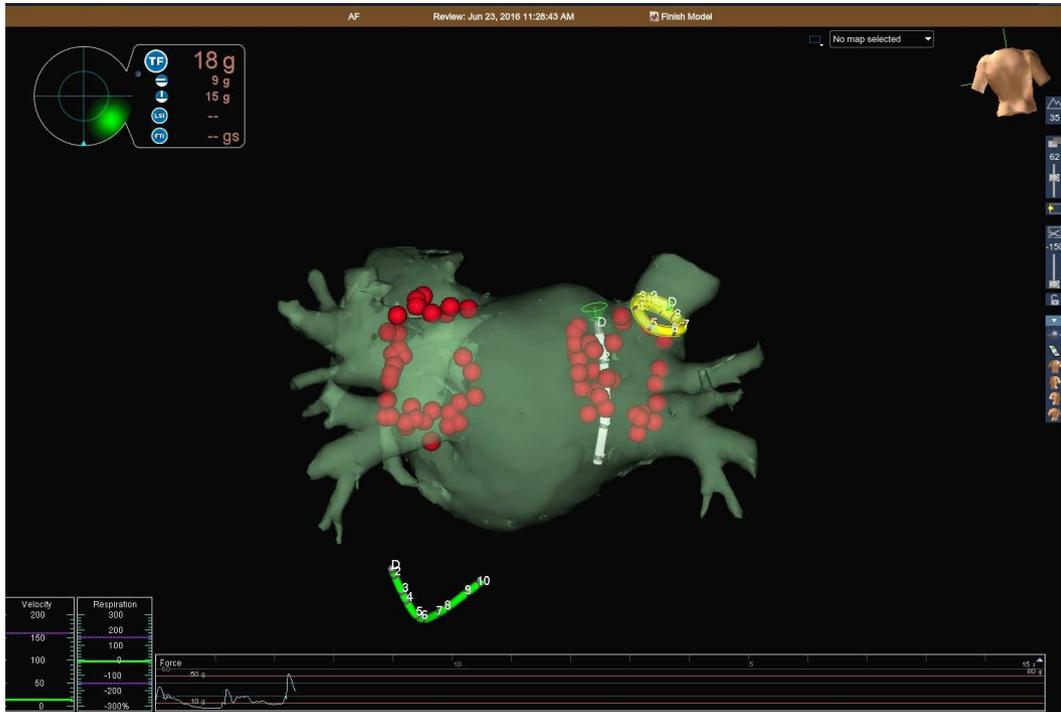
Atrial fibrillation (AF) is the most frequent form of supraventricular arrhythmia in medical practice. It is characterized by chaotic electrical activity in the atria, which often leads to irregular and fast ventricular contractions. Pulmonary veins (PV) play an essential part in the genesis of AF. There are a series of risk factors that trigger the development and recurrence of AF after PV isolation. Despite advanced medical technology, the success rate of AF ablation is not satisfactory. The purpose of this study is to assess the preprocedural imaging and serum biomarkers linked to an increased recurrence of AF after PV isolation. The primary endpoint is represented by AF recurrence after PV isolation. In addition, the rate of cardiovascular death and the rate of major adverse cardiovascular events will be assessed in relation to the enlargement of the left atrium and the volume of epicardial adipose tissue surrounding the heart.

**Keywords:** atrial fibrillation, inflammatory biomarkers, epicardial adipose tissue, atrial volume

## STUDY RATIONALE

Atrial fibrillation (AF) is the most frequent sustained supraventricular arrhythmia, with an increasing prevalence lately.<sup>1</sup> It is characterized by chaotic electrical activity in the atria, which often leads to irregular and fast ventricular contractions. AF has a rising global incidence and prevalence and represents an important public health problem, being associated with increased morbidity and mortality.<sup>2,3</sup>

The initiation of AF requires a “trigger”, which most frequently originates from the pulmonary veins (PV).<sup>4,5</sup> AF begins with paroxysmal episodes that



**FIGURE 1.** Postero-anterior view of the left atrium during the AF ablation. The red tags represent ablation points around the right and left pulmonary veins' ostia. The yellow catheter is the Lasso catheter, which is positioned inside the right superior pulmonary vein. The white catheter is the ablation catheter. The green catheter is placed in the coronary sinus.

cause atrial electrophysiological remodeling that will lead to persistent AF, the so-called “AF begets AF” principle.<sup>6</sup>

According to European recommendations, patients with drug-refractory paroxysmal and persistent AF have a Class I indication for radiofrequency ablation therapy by electroanatomical mapping, which is a complex procedure consisting of electrically isolating the PV from the atrium, through the transeptal approach (Figure 1).<sup>7</sup>

Despite advanced medical technology, the success rate of AF ablation is only 70% in patients with paroxysmal AF and 50% in persistent AF.<sup>8,9</sup> There are a series of risk factors that cause the development and recurrence of atrial fibrillation after isolation of the PV, such as right and left atrial enlargement, epicardial fat, left ventricular dysfunction, and myocardial fibrosis caused by local atrial inflammation.<sup>10–21</sup>

Right and left atrial volume indexed to body surface area plays an important role, representing an independent factor in the recurrence of AF after radiofrequency PV isolation. Serial studies demonstrated that larger left and right atrial volumes are associated with increased recurrence of AF.<sup>17,22–25</sup>

Numerous studies demonstrated that epicardial adipose tissue (EAT) is an independent risk factor that can cause AF, and it has a quantitative association with AF severity.<sup>26–32</sup> EAT is located around the heart, without any

barriers between the myocardium of the atria and the ventricle.<sup>33</sup> Inflammatory mediators and adipokines such as high-sensitivity C-reactive protein (hs-CRP), IL-6, IL-8, IL-1b, and TNF- $\alpha$ , as well as matrix metalloproteinases 2 and 7 secreted by metabolically active EAT, have a significant part in the electrical and structural remodeling of the atrial and ventricular myocardium, thus contributing to the development of left ventricular diastolic dysfunction and AF, respectively.<sup>34–43</sup> Furthermore, there is a strong connection between AF, left ventricular diastolic dysfunction, and elevated levels of NT-pro-BNP.<sup>44–48</sup> It has been demonstrated that an increased NT-pro-BNP level is correlated with a higher recurrence of AF after electrical cardioversion or catheter isolation of PV.<sup>49,50</sup>

## STUDY HYPOTHESIS

This study aims to identify novel serum biomarkers (hs-CRP, NT-pro-BNP) and imaging markers acquired via cardiac computed tomography (epicardial fat volume and the volume of the atria), as predictors of sinus rhythm maintenance after AF ablation using electroanatomical PV isolation. The study will address a new and challenging hypothesis, according to which inflammatory markers could be related to an increased risk of recurrence after AF abla-

tion, at the same time studying the role of a proper selection of patients, based on serum and imaging biomarkers, in preventing the recurrence of AF after radiofrequency ablation.

## STUDY OBJECTIVES

The primary aim of the present study is to analyze novel imaging-derived biomarkers acquired via cardiac computed tomography (CT), such as left and right atrial volume and epicardial adipose tissue volume, in addition to inflammatory biomarkers, correlated with the risk of AF recurrence after the ablation procedure.

### Secondary aims

The study also seeks to identify the relationship concerning the structural remodeling of the left and right atrium, the volumetric assessment of EAT, and the level of serum inflammatory biomarkers.

## MATERIAL AND METHODS

### Study design

This clinical prospective, descriptive research will enroll 50 subjects with AF eligible for catheter ablation. At baseline, imaging biomarkers and laboratory analyses will be acquired prior to ablation, followed by 3D isolation of the pulmonary veins. Follow-up will be performed at 3, 6, and

12 months after catheter ablation, in order to determine the recurrence rate and the evolution of atrial volumes.

Baseline assessment will include physical examination, ECG, echocardiography, cardiac CT, evaluation of risk factors and comorbidities. Serum levels of hs-CRP and NT-pro-BNP will be determined 1 day prior to the ablation procedure. In each case, the presence of an intra-atrial thrombus will be excluded based on cardiac CT or transesophageal echocardiography. The atrial volumes, the anatomy of the pulmonary veins, and the volume of EAT will be determined using cardiac CT (Figure 2). PV isolation will be performed using the EnSite NavX three-dimensional electroanatomical mapping system. A periprocedural fusion of cardiac CT and electroanatomical map of the left atrium will be achieved in order to improve the intraoperative images.

The subjects enrolled in the study will be separated into 2 groups based on the recurrence of AF after ablation at the 1-year follow-up (Figure 3). Patients with AF recurrence will be included in the first category, while the other group will consist of subjects without AF recurrence after ablation.

## INCLUSION AND EXCLUSION CRITERIA

All patients will sign an informed consent before enrolment in the study. The inclusion and exclusion criteria are presented below.

### Inclusion criteria:

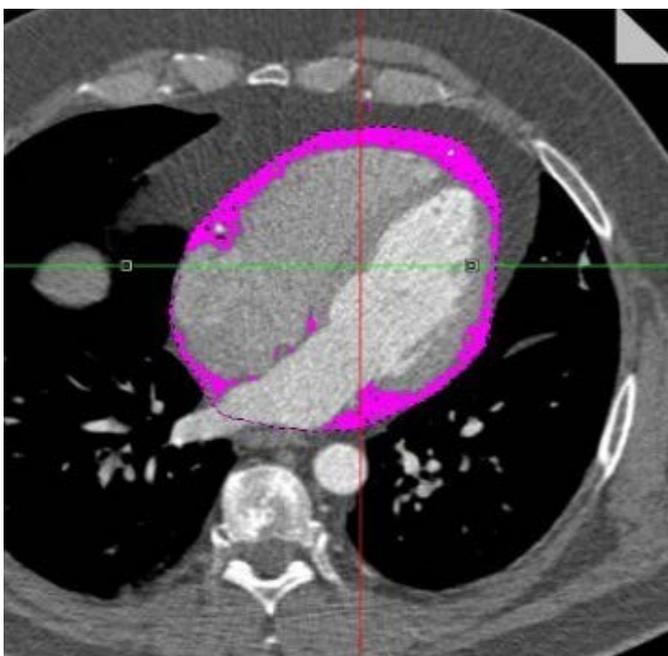
- patients aged at least 18 years;
- patients who have signed the written informed consent;
- patients with non-valvular paroxysmal or persistent AF.

### Exclusion criteria:

- patients' refusal to participate in the study;
- sensitivity to the contrast substance;
- pregnant women;
- acute or chronic renal failure;
- critically ill subjects and patients who may not be compliant to the study procedures or might not undergo follow-up.

## ENDPOINTS

The primary endpoint of the present research is the recurrence of AF after pulmonary vein isolation. In addition,



**FIGURE 2.** Epicardial adipose tissue quantification using native CT



**FIGURE 3.** INFLAMAP study design

cardiovascular death and the proportion of major adverse cardiovascular events (MACE) will be identified in correlation to the enlargement of the atrium and the volume of epicardial fat.

### STATISTICAL ANALYSIS

All statistical data processing will be conducted in the laboratory of medical statistics of the Advanced Cardiac Multimodal Imaging Research Center S.C. Cardio-Med S.R.L.

The CT and the electroanatomical map of the left atrium will be fused in real time throughout the catheter ablation procedure. The calculation of the left and right atrial volumes and the EAT volume will be performed by a radiologist.

### ETHICAL CONSIDERATIONS

All study processes are coherent with the ideologies stated within the Declaration of Helsinki. All the enrolled subjects will sign an informed agreement before inclusion in the study. The study has been approved by the ethics committee of the Cardio Med Medical Center Țirgu Mureș, Romania and of the University of Medicine and Pharmacy of Țirgu Mureș, Romania.

### CONCLUSIONS

In conclusion, this study will identify the subpopulation of patients with AF who can benefit most from the expensive procedures of pulmonary vein isolation, based on a complex panel of biomarkers including serum as well as

novel 3D imaging biomarkers. At the same time, the study will identify the most relevant biomarkers that can serve as predictors for sinus rhythm maintenance during follow-up, after successful ablation of AF.

## CONFLICT OF INTEREST

Nothing to declare.

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