Original Paper

The Significance of Inflammation in Atrial Fibrillation

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ABSTRACT: Aim. The aim of the study was to assess the inflammatory status in individuals diagnosed with atrial fibrillation (Afi) and establish an association between this status and the clinicopathological features. Material and Methods. Our study was conducted retrospectively and initially involved 278 patients. However, after excluding 27 patients, we ultimately ended up with 167 patients who had an inflammatory status and 84 patients who did not have an inflammatory status. These patients were then analyzed. Results. Patients who had inflammation showed higher values for the CHA2DS2-VASc and HAS-BLED scores (P= 0.0132 for CHA2DS2-VASc and P= 0.0024 for HAS-BLED). Also, it was observed that patients with associated inflammation exhibited an increase in both the volume and the area of the left atrium. Patients with hypertension had a higher prevalence of inflammation, with heart failure and with ischemic heart disease. It is worth noting that patients with atrial fibrillation and increased inflammatory status exhibited higher rates of stroke (22.75% vs 10.71% in patients without inflammation, odds ratio = 2.455, 95% confidence interval 1.161 to 5.425, p = 0.0253). Conclusions. Our research has demonstrated that patients diagnosed with atrial fibrillation and exhibiting a heightened inflammatory status also present association with other comorbidities, including hypertension, heart failure, ischemic heart disease, and stroke.

KEYWORDS: *Atrial fibrillation, inflammation, heart failure, stroke.*

Introduction

Atrial fibrillation (AF) is a prevalent and significant condition that is linked to significant illness and death. It leads to a range of potentially severe complications, including heart failure (HF), different types of cardiovascular disorders, and especially stroke [1,2].

At present, a wide range of treatment modalities exists for the management of atrial fibrillation. Despite the importance of these approaches, it is important to take into considerantion that they have limitations and potential adverse effects, creating a significant gap in the field of therapeutic innovation [3].

These strategies refer to the use of antiarrhythmic medications in order to sustain a normal sinus rhythm, bradycardic agents in order to regulate increased heart rate, and nevertheless, anticoagulant medications in order to reduce the risk of stroke.

Furthermore, ablation procedures are seen as important therapeutic advancement in facilitating the preservation of sinus rhythm [1,3].

The role of inflammation in atrial fibrillation has been studied for more than two decades, and subsequent research has demonstrated its substantial evidence [4].

The main link between inflammation and atrial fibrillation is characterized by accelerated atrial activity that is not coordinated with irregular ventricular activity during fibrillation.

This conducts to an elevation in the parietal stress of the atria, resulting in stretching and a significant decrease in cardiac output [4-6].

Activating the production of angiotensin II by renin-angiotensin-aldosterone system is triggered by hypoperfusion of the hormonal regulatory organs and the atrial stretch.

Therefore, a change in the endothelium takes place, resulting in a modified hemodynamic rheology, leading to the recruitment of inflammatory cells that release cytokines [4-6].

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However, an increasing amount of research is now connecting inflammation and atrial fibrillation to a variety of cardiovascular diseases, including diabetes and hypertension, ischemic heart disease, heart failure, chronic kidney disease and hypertension or insulin resistance [6-11].

Nevertheless, the efficacy of conventional anti-inflammatory agents in managing atrial fibrillation has typically been limited and lacks compelling evidence [1].

Furthermore, alongside the conventional perspective positing that inflammation arises from the synthesis of cytokines by various infiltrating leukocytes in reaction to tissue injury, an alternative viewpoint suggests that other cell types, such as cardiomyocytes, may possess significant inflammatory capabilities in signaling, thereby contributing to tissue pathology and remodeling.

Our study aimed at assessing patients with atrial fibrillation who exhibited increased inflammation without any additional secondary inflammatory processes, and to investigate the correlation between this inflammation and the clinicopathological features.

Material and Methods

We conducted a retrospective study initially involving 278 patients, but subsequently reduced the sample size to 251 patients by excluding 27 patients.

To mitigate bias, patients were included in a sequential manner.

Atrial fibrillation was the primary criterion for inclusion.

Subsequently, the patients were categorized into two groups based on the presence or absence of the inflammatory status, which was determined by a value exceeding the upper threshold of the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), or fibrinogen.

Figure 1 illustrates the study design.

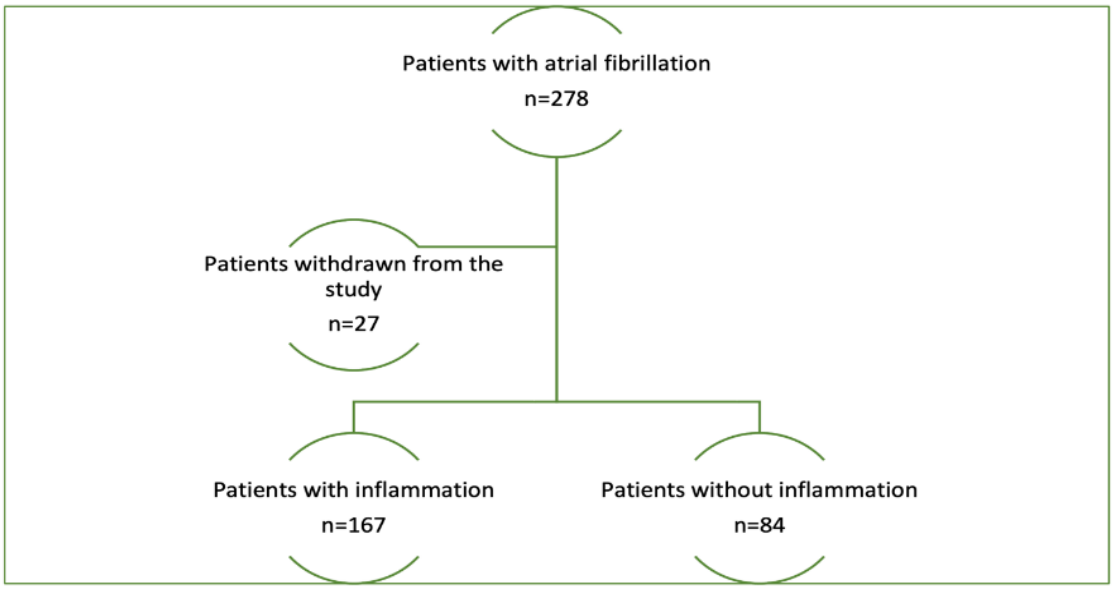

Figure 1. Design of the study.

The data of the patients were extracted from the medical records of the Timisoara Municipal Emergency Clinical Hospital and the Timisoara Cardiovascular Disease Institute, spanning the period from January 2020 to December 2023. The research proposal received approval from the Ethics Committee of the University of Medicine and Pharmacy 'Vitor Babes', Timisoara, Romania, under the reference number 82/2020.

The study population consisted of individuals who were diagnosed with atrial fibrillation, which could be categorized as paroxysmal, persistent, or permanent, either at the time of assessment or had a documented medical history of atrial fibrillation. A 12-lead electrocardiogram, rhythm strip, or Holter electrocardiogram was utilized to document the presence of atrial fibrillation. The atrial fibrillation lasted for a minimum of 30 seconds. The inclusion criteria for this study included individuals aged 18 years and above, as well as their willingness to consent to the utilization of their medical records for purposes of scientific investigation.

Exclusion criteria were employed in our study, including the presence of autoimmune diseases, systemic or local inflammatory diseases, documented infections, congenital heart diseases, significant severe oncological, liver, or

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hematological diseases, as well as acute cardiac pathologies such as heart attack, acute myocardial infarction, cardiac arrest, electrical or hemodynamic instability with cardiogenic shock, or mechanical complications. The exclusion criteria were expanded to include acute cardiogenic pulmonary edema, massive pulmonary thromboembolism, and end-stage heart failure.

The primary data extracted from the patients' medical records included age, gender, CHA_2DS_2-VASc and HAS-BLED scores, presence of hypertension, ischemic heart disease, heart failure, dyslipidemia, stroke, as well as biological tests including NT-proBNP, ESR, CRP, and fibrinogen. These measurements were obtained upon patients' admission to the emergency department and throughout the time they were hospitalized. The primary echocardiographic parameters employed in our investigation encompassed the left ventricular ejection fraction (LVEF), accompanying parameters related to the characterization of the left atrium, including volume, area, trapezoidal shape, and ejection fraction (Figure 2).

We utilized an ultrasound machine that was equipped with specialized software for analyzing the left atrium. Specifically, we employed a GE VIVID E95 machine (Vivid E95, GE Health Medical, Milwaukee, WI, USA) that allowed for simultaneous recording of electrocardiograms (ECGs).

Figure 2. Representative image with the analysis mode of the left atrium (blue line).

Statistical analysis

The study's data was loaded using Microsoft Office Excel 2019 (Microsoft Corporation, Redmond, Washington, DC, USA) and subsequently subjected to statistical analysis with GraphPad software (Version 10.2.2., CA, USA).

This study utilized the Fisher exact test to conduct a comparative analysis of proportions. Consequently, for the identified risk factors, the odds ratio was determined. The student t-test was employed to compare the means of two groups.

In all instances, a threshold of significance of $P < 0.05$ was chosen as indicative of statistical significance.

Results

The sample size for our study consisted of 251 patients, who were categorized into two groups: one group (n=167) with atrial fibrillation and an associated inflammatory status, and another group (n=84) with atrial fibrillation and no associated inflammatory status.

Inflammation was characterized by an elevation in the erythrocyte sedimentation rate (ESR), C-reactive protein, or fibrinogen levels beyond the predefined limits, as depicted in Figure 3.

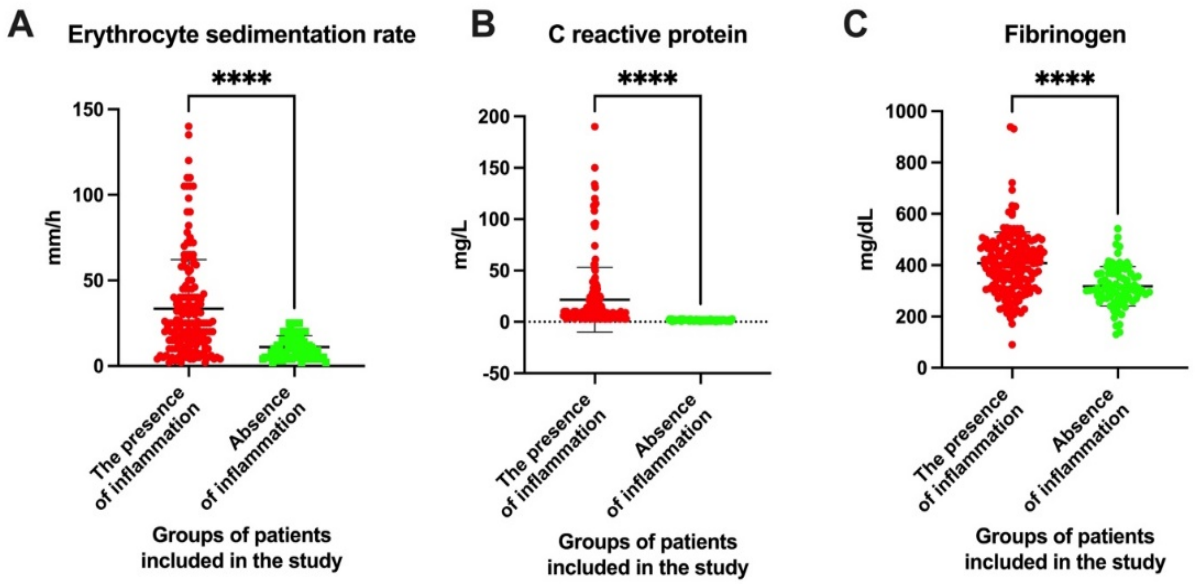

Figure 3. The biological samples' values to assess the inflammatory status. The parameters of interest in this study are A - erythrocyte sedimentation rate (ESR), B - C-reactive protein, and C - fibrinogen. * represents the highly significant statistical difference.***

A significant correlation was found between the inflammatory status of older patients (mean age 73.13±9.090 years) vs younger patients (69.69±8.359 years, P= 0.0042), as depicted in Figure 4A.

Patients who also had inflammation showed higher values for the CHA_2DS_2-VASc and HAS-BLED scores (Figure 4, B and C) (P= 0.0132 for CHA2DS2-VASc and P= 0.0024 for HAS-BLED).

In relation to the parameters of the left atrium, it was observed that patients with associated inflammation exhibited an increase in both the volume (142.2±53.87 mL vs 127.8±51.02 mL, P=0.0450) and the area of the left atrium (35.12± 9.070 cm2 vs 32.53±8.600 cm2, P=0.0332) (Figure 4, D and G).

Conversely, a higher inflammatory status was linked to both the lower left atrial ejection fraction (Figure 4E) and the lower left ventricular ejection fraction (Figure 4F).

Finally, it is worth noting that patients with atrial fibrillation and simultaneous inflammatory status exhibited a significantly higher NT-proBNP value (4403±533 pg/mL vs 2112±391.6 pg/mL, P=0.0032), as depicted in Figure 4H.

Patients with hypertension had a higher prevalence of inflammation (98.20% vs 91.67% without inflammation, odds ratio = 4.970, 95% confidence interval 1.326 to 17.94, p = 0.0181).

Patients with heart failure had a higher percentage of patients with inflammatory status (85.63% vs 73.81% without inflammation, odds ratio = 2.114, 95% confidence interval 1.115 to 4.126, p = 0.0256).

Furthermore, it was observed that patients with atrial fibrillation and inflammatory status exhibited a greater prevalence of ischemic heart disease (83.33% compared to 16.67% in patients without inflammation, odds ratio = 2.992, 95% confidence interval 1.364 to 6.378, p = 0.0062).

Finally, it is worth noting that patients with atrial fibrillation and increased inflammatory status exhibited higher rates of stroke (22.75% vs 10.71% in patients without inflammation, odds ratio = 2.455, 95% confidence interval 1.161 to 5.425, p = 0.0253).

Figure 5 demonstrates that there were no correlations observed between the gender of the patients, the type of atrial fibrillation, the presence of diabetes or dyslipidemia, and the shape of the left atrium.

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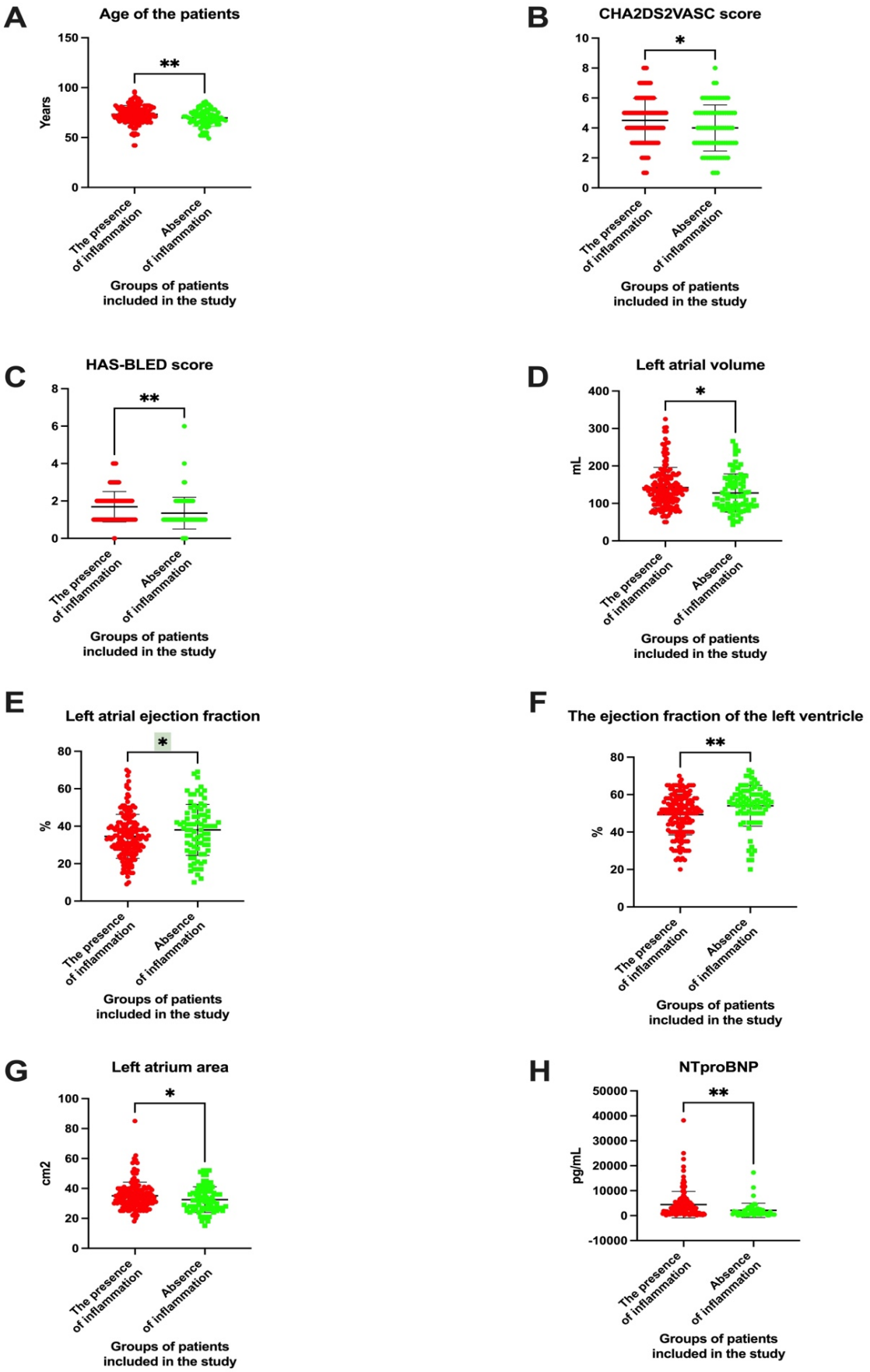

Figure 4. Clinicopathological features for the patients included in our study. A- Age of the patients, B- CHA_2DS_2-VASc score, C- HAS-BLED score, D- left atrial volume, E- left atrial ejection fraction, F- left ventricle ejection fraction, G- left atrium area, H- NTproBNP value. *P<0.05. **P<0.01

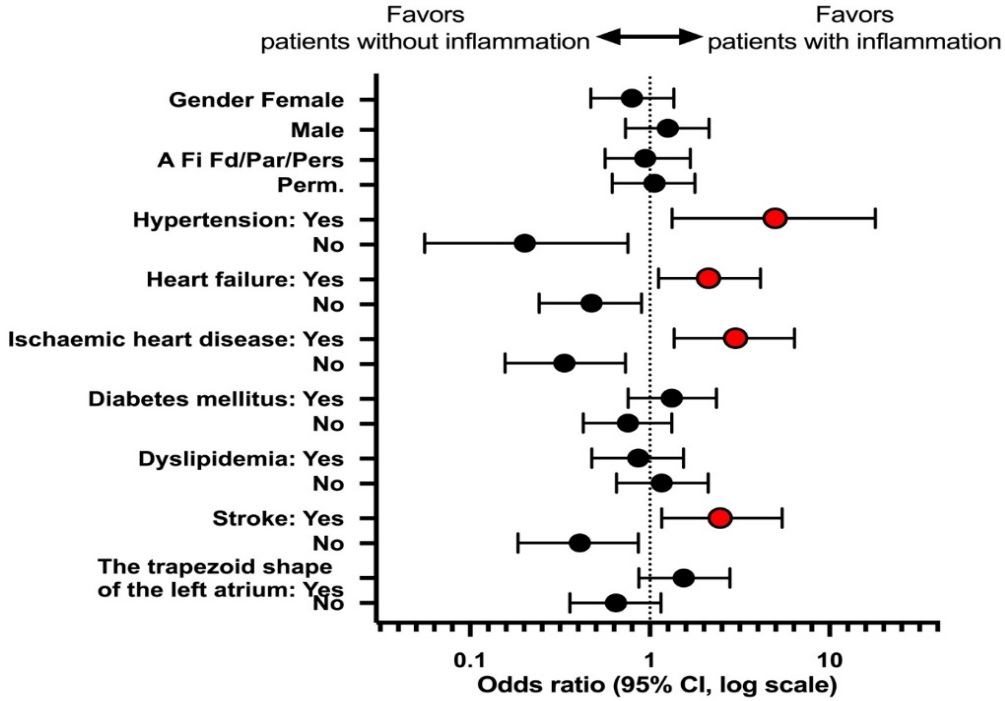

Figure 5. Odds ratio (OR) and its inverse. CI stands for confidence interval. A Fi - atrial fibrillation. Fd - First diagnosed, Parox - Paroxysmal, Pers - Persistent. Red color - P < 0.05.

Discussions

Despite the recent publication of a diagnosis and treatment guide for atrial fibrillation by the European Society of Cardiology, there remains a lack of comprehensive understanding regarding the etiopathogenesis and therapeutic approaches associated with this disease [12].

Historical evidence suggests a connection between atrial fibrillation and inflammation, as AF is often linked to inflammatory conditions of the heart wall, such as pericarditis or myocarditis [13,14].

The hypothesis of inflammation in atrial fibrillation was initially formulated by Bruins and his team of researchers. This hypothesis was based on their observations of a higher occurrence of atrial fibrillation in patients who had undergone coronary bypass surgery. According to their description, the highest occurrence of atrial fibrillation was observed on the second- and third-day following bypass surgery, coinciding with the most significant rise in C-reactive protein levels [15].

Maixent et al. conducted a study wherein it was observed that a considerable proportion of patients with idiopathic paroxysmal atrial fibrillation exhibited circulating autoantibodies targeting myosin heavy chain. These data refer to the potential involvement of an autoimmune inflammatory mechanism in certain individuals with paroxysmal atrial fibrillation [16].

Recent research has proved the existence of a correlation between atrial fibrillation and systemic inflammation in individuals suffering from diverse autoimmune disorders, including psoriasis, rheumatoid arthritis, and sepsis [17-20].

It is important to take into account that the occurrence of newly diagnosed atrial fibrillation in patients with sepsis varies from 1.9% to 40%. Furthermore, in patients suffering from severe sepsis or septic shock, the incidence of atrial fibrillation is higher compared to patients with a less severe form of sepsis [18].

This condition has been associated with several risk factors such as advanced age, male gender, renal failure, white ethnicity, obesity, and chronic liver disease [1].

The exclusion of cardiovascular comorbidities should be noted in relation to these conditions [1].

Moreover, individuals diagnosed with sepsis who experienced the onset of atrial fibrillation for the initial time presented a high susceptibility to stroke and an elevated mortality rate within hospitalization. The previously mentioned cohort of patients also associated enduring risks, including the need for hospitalization due to heart failure or ischemic stroke [1].

Research on animal models with systemic or local inflammation has demonstrated an

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important association between inflammation and the development of atrial fibrillation. An example in this sense are the animals with sepsis, which exhibited atrial infiltration accompanied by macrophages and CD68+ cells. Subsequently, this group of animals registered a high incidence of atrial fibrillation when exposed to specific pacing protocols [21,22].

An additional animal model of sepsis is exemplified by animals in which sepsis was induced through the administration of lipopolysaccharide (LPS). These animals present a decrease in the duration of the action potential and the effective atrial refractory period by reducing the current of Ca2+ through L-type channels. This observation highlights a potential mechanism involved in the development of atrial fibrillation [23].

Furthermore, sepsis can be linked to delayed afterdepolarizations and triggered activity. This can be linked to an elevation in Ca2+/calmodulin-dependent protein kinase II levels in the atrium and the hyperphosphorylation of cardiac ryanodine receptor 2 (RYR2) channels. These pathophysiological mechanisms have been studied in the context of atrial fibrillation [24].

Animals suffering from pericarditis can also experience atrial fibrillation even in the absence of pathogenic microorganisms. In the case of these animals disgnosed with experimental pericarditis, the duration of the action potential and the effective atrial refractory period are significantly reduced. This reduction in atrial refractory period leads to an increase in atrial ectopy, which in turn sustains atrial fibrillation [25].

Fibrosis together with atrial structural remodeling, cardiomyocyte hypertrophy, and atrial interstitial fibrosis were noticed on histological pieces. Nevertheless, the acute phase of experimental pericarditis did not cause an important increase in atrial fibrillation inducibility [25].

In what C-reactive protein (CRP) levels are concerned, it can be taken into account that this inflammatory biomarker is characterized by its non-specific nature and it exhibits a high degree of reproducibility. Liver is the main source of synthesis. It is primarily produced there in response to inflammatory cytokines. Research findings mentioned in the literature indicate that individuals diagnosed with atrial fibrillation exhibit elevated levels of C-reactive protein (CRP) in their bloodstream in comparison to those without a prior history of atrial fibrillation. Moreover, patients with persistent atrial fibrillation present higher CRP levels in comparison to those suffering from paroxysmal AF [26].

Elevated levels of circulating C-reactive protein (CRP) seemed to be linked to the reoccurrence of atrial fibrillation following electrical cardioversion, as well as following catheter ablation [27].

In patients with atrial fibrillation, there is a positive correlation between CRP levels and stroke risk factors including diabetes and hypertension, as presented in our study [28].

Limitations of the study

The main limitation of our study is represented by the retrospective nature of the analysis, as well as the relatively limited sample size of patients included in the examination of a potential correlation between atrial fibrillation and inflammatory status. Furthermore, despite the presence of multiple exclusion criteria, our study did not identify a potential etiology for the demonstrated inflammatory condition.

Conclusions

Our research has proved that individuals suffering from atrial fibrillation and exhibiting a heightened inflammatory status also present other comorbidities such as hypertension, heart failure, ischemic heart disease, chronic kidney disease and stroke. These data suggest a newdirection for investigations that involve elucidating molecular mechanisms responsible for the findings in our study, as well as evaluating the efficacy of novel anti-inflammatory drugs in order to ameliorate the pathological conditions associated with our study and, nevertheless, to reduce burden of atrial fibrillation.

Conflict of interests

None to declare.

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