DE GRUYTER OPEN

Journal of Interdisciplinary Medicine

ORIGINAL RESEARCH

CARDIOLOGY // HEMATOLOGY

Imaging-derived Biomarkers Associated with Atrial FIBROsis, Structural Remodeling and the Risk of Cardio-embolic Events in Patients with Atrial Fibrillation – the FIBROS Study

Balázs Oltean-Péter[1,3], Szilamér Korodi[1,2], István Benedek Jr[1,3], Erzsébet Lázár[1,3], Johanna Kéri[1,3], Annamária Pakucs[1,3], István Kovács[1,2], Lehel Bordi[1,2], Adriana Mitre[1], Imre Benedek[1,2], Theodora Benedek[1,2], István Benedek[1,3]

[1] University of Medicine and Pharmacy, Tîrgu Mureș, Romania
[2] Center of Advanced Research in Multimodality Cardiac Imaging, Cardio Med Medical Center, Tîrgu Mureș, Romania
[3] Clinic of Hematology and Bone Marrow Transplantation Unit, Tîrgu Mureș, Romania

CORRESPONDENCE

Szilamér Korodi
Str. Gheorghe Marinescu nr. 38
540139 Tîrgu Mureș, Romania
Tel: +40 265 215 551
E-mail: szilamerkorodi@yahoo.com

ARTICLE HISTORY

Received: October 7, 2017
Accepted: November 11, 2017

Balázs Oltean-Péter • Str. Gheorghe Marinescu nr. 38, 540139 Tîrgu Mureș, Romania. Tel: +40 265 215 551
István Benedek Jr • Str. Gheorghe Marinescu nr. 38, 540139 Tîrgu Mureș, Romania. Tel: +40 265 215 551
Erzsébet Lázár • Str. Gheorghe Marinescu nr. 38, 540139 Tîrgu Mureș, Romania. Tel: +40 265 215 551
Johanna Kéri • Str. Gheorghe Marinescu nr. 38, 540139 Tîrgu Mureș, Romania. Tel: +40 265 215 551
Annamária Pakucs • Str. Gheorghe Marinescu nr. 38, 540139 Tîrgu Mureș, Romania. Tel: +40 265 215 551
István Kovács • Str. Gheorghe Marinescu nr. 38, 540139 Tîrgu Mureș, Romania. Tel: +40 265 215 551
Lehel Bordi • Str. Gheorghe Marinescu nr. 38, 540139 Tîrgu Mureș, Romania. Tel: +40 265 215 551
Adriana Mitre • Str. Gheorghe Marinescu nr. 38, 540139 Tîrgu Mureș, Romania. Tel: +40 265 215 551
Imre Benedek • Str. Gheorghe Marinescu nr. 38, 540139 Tîrgu Mureș, Romania. Tel: +40 265 215 551
Theodora Benedek • Str. Gheorghe Marinescu nr. 38, 540139 Tîrgu Mureș, Romania. Tel: +40 265 215 551
István Benedek • Str. Gheorghe Marinescu nr. 38, 540139 Tîrgu Mureș, Romania. Tel: +40 265 215 551

ABSTRACT

Recent studies demonstrated that despite restoration of the sinus rhythm, patients with a positive history of atrial fibrillation (AF) are still at risk of thromboembolic events. The primary objective of this study is to identify new imaging-derived biomarkers provided by modern imaging technologies, such as cardiac computed tomography angiography, delayed enhancement magnetic resonance imaging, or speckle tracking echocardiography, as well as hematological biomarkers, associated with the risk of intracavitary thrombosis in patients with AF, in order to identify the imaging-derived characteristics associated with an increased risk of cardio-embolic events. Imaging data collected will be post-processed using advanced techniques of computational modeling, in order to fully characterize the degree of structural remodeling and the amount of atrial fibrosis. The primary endpoint of the study is represented by the rate of thromboembolic events. The rate of cardiovascular death, the rate of major adverse cardiovascular events, and the rate of AF recurrence will also be determined in relation to the degree of structural remodeling and atrial fibrosis.

Keywords: atrial fibrillation, atrial fibrosis, inflammation, coagulation, stroke, thrombosis, magnetic resonance, ablation

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia that can appear in patients with or without cardiac comorbidities.[1] The incidence of AF is decreasing; however, its prevalence remained constant, one third of the adult population being affected by this devastating disease.[2,3] The risk of stroke in patients with AF decreased in the last few years; however, this was not accompanied by a decrease in mortality risk.[2] Recent studies have demonstrated that despite sinus rhythm restoration, patients with a positive history of AF are still at risk of thromboembolic events. Therefore, blood stagnation in the atria is not the only contributor to the development of intracavitary thrombosis.[4–6] In the ASSERT study, only 8% of patients with stroke or systemic embolism had atrial fibrillation in the last 30 days prior to the embolic event.[7] Along with atrial stasis, several mechanisms are involved in the pathogenesis of atrial thrombosis in AF such as atrial fibrosis, epicardial adiposity,[8,9] local inflammation, hypercoagulability,[10] endothelial dysfunction, structural pathologies, neurohumoral and genetic factors.[4] It has been described in the literature that atrial fibrosis significantly increases the incidence of stroke, and that the degree of atrial fibrosis is significantly higher in patients with stroke.[7] Figure 1 presents the main factors involved in the pathophysiology of AF and the link between AF and stroke.

Atrial fibrosis plays an important role in the appearance, maintenance, and recurrence of AF and in the effectiveness of catheter ablation. At the same time, atrial fibrosis is a consequence of AF, showing a vicious circle in which "AF begets AF".[11] Atrial fibrosis can be caused by: atrial fibrillation, rapid atrial myocyte depolarization,[12] inflammation, mechanical stretch, atrial distension,[13] cardiac injury,[11] electrical derangements,[11] accumulation of intracellular Ca ions, autocrine and paracrine mediators,[12] oxidative stress,[14] diabetes, obesity,[15] hypercoagulability (activation of PAR1 receptors by thrombin),[16] genetic factors and systemic autoimmune disease. Cardiovascular comorbidities and age (<75 years) did not appear to correlate with the degree of atrial fibrosis.[17] Atrial fibrosis can be noninvasively assessed and quantified using delayed enhancement magnetic resonance imaging (DE-MRI).[18]

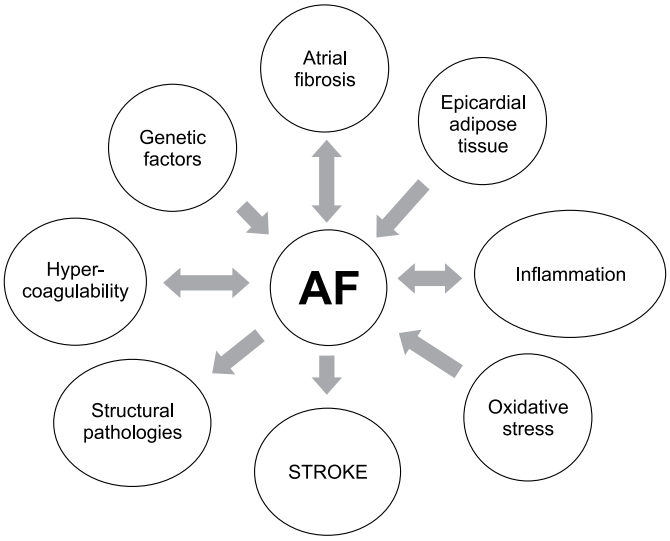

FIGURE 1. Mechanisms involved in the determinism of atrial fibrillation and associated stroke

Inflammation can be a cause or a consequence of AF. A correlation between AF and circulatory levels of inflammatory biomarkers, such as C-reactive protein (CRP), cytokines, interleukin, complement, and activation state of leukocytes and atrial fibrillation has been documented.[19,20] The link between inflammation and AF includes atrial fibrosis as a main component. Inflammation increases the level of pro-inflammation cytokines in the blood, such as IL 1, IL 2, IL 6, IL 8, CRP, tumor necrosis factor α, monocyte or chemoattractant protein 1, which stimulate endothelial and other cells.[19] An independent correlation between the level of inflammatory biomarkers and AF was described, the level of CRP and IL 6 correlating with structural remodeling (left atrium enlargement) and with impaired left atrium (LA) function.[21] Furthermore, the level of CRP is an independent predictor of AF, and this level is higher in patients with persistent AF.[19] Inflammation also has an important role in thrombus formation and ischemic events, this correlation being mediated by endothelial injury, platelet activation, tissue factors, von Willebrand factor, fibrinogen, and P-selectin.[22,23] Therefore, CRP can become a useful biomarker to assess the risk of thromboembolic events in patients with AF.[12]

Pericardial adipose tissue is a highly metabolically active tissue that can predispose to AF, involving inflammatory cytokines and oxidative stress. Furthermore, it has a quantitative association with the severity of AF.[24,25]

AF produces a hypercoagulable state. Thrombin can initiate a pro-fibrotic, pro-inflammatory, and pro-hypertrophic state via stimulation of protease-activated receptors.[26] New anticoagulant therapy can inhibit PAR1 activation and through it can prevent the development of a substrate for AF.[27]

A CHADS2 and CHA2DS2-VASC score of 0 may be insufficient to avoid thromboembolism events in patients with AF.[28] More information about thromboembolic risk can be obtain by determination of the level of troponin I, CRP, and NT-pro BNP.[29] However, even these hematological biomarkers fail to fully predict the risk of thromboem-

bolism.[28] Novel studies demonstrated that AF and atrial fibrosis are independent risk factors for stroke, even after the sinus rhythm has been restored. A degree IV (>75%) atrial fibrosis can have a huge impact on the risk of stroke and may be included in the new stroke prediction index.[13]

POTENTIAL CONTRIBUTIONS OF THE STUDY

The phenomenon of atrial fibrosis as a pathogenic mechanism of AF has been described in the literature; however, its role in atrial thrombosis has not been elucidated so far.

The originality of the present study consists in building an algorithm of investigation by which high-quality imaging data will be correlated with hematological markers of inflammation, platelet aggregation, and clotting. A model of complex investigations will be developed to identify patients with increased thromboembolic risk, and thus a large number of cardio-embolic events will be prevented.

STUDY HYPOTHESIS

The degree of atrial fibrosis and the level of inflammatory markers in the blood can predict the risk of thromboembolic events in patients with atrial fibrillation.

STUDY OBJECTIVES

Primary objective

The primary objective of this study is to identify new imaging-derived biomarkers provided by modern imaging technologies such as cardiac computed tomography angiography (CCTA), delayed enhancement MR imaging (DE-MRI), or speckle-tracking echocardiography (STE), as well as hematological biomarkers, associated with the risk of intracavitary thrombosis in patients with AF, in order to identify the characteristics associated with an increased risk of cardio-embolic events.

Secondary objectives

This study also aims to evaluate the correlation between the structural remodeling of the left and right atria and the amount of myocardial fibrosis of the left atrium, using DE-MRI. We will determine the function of the left atrium using exercise stress test (EST) and the automated quantification of atrial fibrosis using dedicated software.

At the same time, volumetric assessment of epicardial adipose tissue will be performed in each patient undergoing CCTA and MRI.

We will also look for identification of hematological biomarkers of predisposition for thrombosis and platelet aggregation and evaluate the differences between these biomarkers in blood samples collected from a peripheral line and from the left atrium during interventional ablation procedures. Another important part of this study is to analyze the electrical remodeling of the atrium using a three-dimensional electro-anatomic mapping system and to correlate these findings with the rate of thrombosis and with the level of local hematological markers. We will determine the rate of recurrence of AF, the rate of thromboembolic events, and the rate of major adverse cardiovascular events (MACE), every 3 months during the follow-up.

METHODS

Study design

This is a prospective, descriptive, cohort study composed of two major parts. In the first part of the study, laboratory tests and necessary interventions will be performed. The second part is represented by the follow-up of patients for 2 years and will contain the analysis of the data obtained during the first part of study. After evaluating eligibility for the screening process, patients who meet the inclusion criteria without exclusion criteria will be included in the study. The study population will be comprised of a minimum of 50 patients. Each patient included in the study will need to be eligible for catheter ablation. Based on the degree of atrial remodeling (size, wall thickness, and function) assessed with CCTA, the study population will be divided in 2 groups. Patients with mild atrial remodeling will be enrolled in the first group, while the second group will contain patients with moderate or severe atrial remodeling.

Personal data of patients will be collected at the start of study. Anamnesis, physical examination, ECG, evaluation of risk factors and comorbidities will be performed in each case. Lab tests will include the level of leukocytes, hs-CRP, and the erythrocyte sedimentation rate. In each case we will exclude the presence of an intracavitary thrombus using transthoracic and transesophageal echocardiography. The structure of atrial anatomy and the level of epicardial adipose tissue will be examined with echocardiography and CCTA. EST will be used for the assessment of cardiac function. Electrophysiological study will be performed in each patient included in the study and the images obtained with CCTA will be merged with the electrical map of the heart.

After trans-septal puncture, but before pulmonary veins isolation, we will harvest blood from the left atrium to determine the level of pro-inflammatory and pro-coagulation

factors. We will quantify the level of hs-CRP, IL-1,6, fibrinogen, tumor necrosis factor, the erythrocyte sedimentation rate, INR, PT, and PT%. At the same time, these factors will be determined from the peripheral blood.

The degree of atrial fibrosis will be assessed using DE-MRI. Upon discharge, we will perform a new ECG to confirm the success of cardioversion. All patients without AF at discharge will be followed-up for 2 years. Patients will be recalled for periodic investigations (anamnesis, physical examination, ECG, echocardiography) in the 3rd, 12th and 24th month and contacted by phone in the 6th and 9th month after cardioversion. At the last session (month 24), MRI and EST will be performed to assess the progression of atrial fibrosis and the changes in atrial function.

INCLUSION AND EXCLUSION CRITERIA

Patients are eligible if they had non-valvular paroxysmal or persistent AF. All patients need to be adults and be able to read and understand the informed consent document. The study cannot be carried out without imaging techniques, therefore patients who present contraindications to imaging tests will be excluded from the study. These conditions are represented by claustrophobia, hypersensitivity to contrast agents (gadolinium, CT contrast agents), pregnancy, acute or chronic kidney failure (stage 3a, 3b, 4, 5), and decompensated cirrhosis. The presence of metallic foreign bodies or cardiac rhythm device are contraindications for magnetic resonance imaging and therefore for the study.

Patients receiving any drug that may affect the level of hematological markers will be excluded from the study. Terminally ill patients and those who may not adhere or may not complete follow-up or do not have reliable information will be also excluded from the study.

ENDPOINTS

The primary endpoint of the study is represented by the rate of thromboembolic events. The rate of cardiovascular death, the rate of MACE, and the rate of AF recurrence will also be determined in relation to the degree of structural remodeling and atrial fibrosis.

DATE STORAGE AND ANALYSES

A dedicated database with the patients' data and imaging tests will be created and handled with the utmost accuracy and confidentiality, only the staff involved in the research having access to this database. Imaging data stored in the database will undergo complex post-processing in the computational medicine laboratory, using computational simulations and advanced imaging techniques processing. The merging of images obtained with CT scanner with the electro-anatomical map of the left atrium will be performed in real time during the catheter ablation procedure. The quantification of the left atrium fibrosis will be performed by a radiologist.

The statistical analysis will be performed in the medical statistics laboratory of the Center of Advanced Research in Multimodal Cardiac Imaging of SC Cardio Med SRL.

ETHICS

All study procedures are in line with the principles of the Declaration of Helsinki. All patients will sign an informed consent prior to be enrolled in the study. The study received Ethics approval from both institutional boards (approval no 28/28.12.2017 from the Ethics Committee of Cardio Med Medical Center, and approval no. 348/13.12.2017 from the Ethics Committee of the University of Medicine and Pharmacy of Tîrgu Mureș).

CONCLUSION

In AF undergoing complex ablation procedures, the rate of recurrence and the cardioversion succession rate are influenced by several intra- and extra-cardiac factors. Novel studies have shown that in addition to atrial stasis, many factors are involved in the appearance of intra-atrial thrombosis. Patients with positive history of AF have also an increased risk for stroke compared to those who never had atrial fibrillation. It is known that atrial fibrosis, inflammation, and hypercoagulability have an important role in the appearance of intracavitary thrombosis, but the exact mechanisms involved in this correlation have not been elucidated so far. This study will characterize new imaging-derived biomarkers to correlate the structural remodeling and fibrosis of the left and right atrium with the hematological parameters reflecting a high coagulability in the atria, in order identify new tools for predicting the risk of thromboembolic events in patients with AF.

ACKNOWLEDGEMENT

This clinical trial is a part of the project entitled "High performance multimodal MRI/CT imaging platform, for applications in computational medicine, nanoparticles and hybrid imaging for the research of atherothrombotic disorders – CARDIO IMAGE". The research is also receiving

funding from the University of Medicine and Pharmacy of Tîrgu Mureș, Romania, via governmental funds for PhD studies.

CONFLICT OF INTEREST

Nothing to declare.

REFERENCES

1. Miyasaka Y, Barnes ME, Gersh BJ, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation*. 2006;114:119-125.
2. Chamberlain AM, Gersh BJ, Alonso A, et al. Decade-long trends in atrial fibrillation incidence and survival: a community study. *Am J Med*. 2015;128:260-267.
3. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation*. 2014;129:837-847.
4. Benjamin J. Hirsh, MD, Robert S, et al. Fibrotic Atrial Cardiomyopathy, Atrial Fibrillation, and Thromboembolism. *Elsevier*. 2015;65:2239-2251.
5. Disertori M, Franzosi MG, Barlera S, et al. Thromboembolic event rate in paroxysmal and persistent atrial fibrillation: data from the GISSIAF trial. *BMC Cardiovasc Disord*. 2013;13:28.
6. Steinberg BA, Hellkamp AS, Lokhnygina Y, et al. Higher risk of death and stroke in patients with persistent vs. paroxysmal atrial fibrillation: results from the ROCKET-AF trial. *Eur Heart J*. 2015;36:288-296.
7. Healey JS, Connolly SJ, Gold MR, et al. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med*. 2012;366:120-129.
8. Haemers P, Hamdi H, Guedj K, et al. Atrial fibrillation is associated with the fibrotic remodelling of adipose tissue in the subepicardium of human and sheep atria. *Eur Heart J*. 2017;38:53-61.
9. Auer J. Fat: an emerging player in the field of atrial fibrillation. *Eur Heart J*. 2017;38:62-65.
10. Luscher FT. Atrial fibrillation beyond the arrhythmia: hypercoagulability, adipose tissue, and fibrotic remodeling. *Eur Heart J*. 2017;38:1-3.
11. Nattel S, Harada M. Atrial remodeling and atrial fibrillation: recent advances and translational perspectives. *J Am Coll Cardiol*. 2014;63:2335-2345.
12. Tan AY, Zimetbaum P. Atrial fibrillation and atrial fibrosis. *J Cardiovasc Pharmacol*. 2011;57:625-629.
13. Mikhail S. Dzeshka, Gregory Y.H. Lip, et al. Cardiac Fibrosis in Patients With Atrial Fibrillation. *JACC*. 2015;66:943-959.
14. Filgueiras-Rama D, Price NF, Martins RP, et al. Long-term frequency gradients during persistent atrial fibrillation in sheep are associated with stable sources in the left atrium. *Circ Arrhythm Electrophysiol*. 2012;5:1160-1167.
15. Gramley F, Lorenzen J, Jedamzik B, et al. Atrial fibrillation is associated with cardiac hypoxia. *Cardiovasc Pathol*. 2010;19:102-111.
16. Steffel J, Luscher TF, Tanner FC. Tissue factor in cardiovascular diseases: molecular mechanisms and clinical implications. *Circulation*. 2006;113:722-731.
17. Daccarett M, Badger TJ, Akoum N, et al. Association of left atrial fibrosis detected by delayed-enhancement magnetic resonance imaging and the risk of stroke in patients with atrial fibrillation. *J Am Coll Cardiol*. 2011;57:831-838.
18. Spragg DD, Khurram I, Nazarian S. Role of Magnetic Resonance Imaging of Atrial Fibrosis in Atrial Fibrillation Ablation. *Arrhythm Electrophysiol Rev*. 2013;2:124-127.
19. Chung MK, Martin DO, Sprecher D, et al. C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. *Circulation*. 2001;104:2886-2891.
20. Mihm MJ, Yu F, Carnes CA, et al. Impaired myofibrillar energetics and oxidative injury during human atrial fibrillation. *Circulation*. 2001;104:174-180.
21. Conen D, Ridker PM, Everett BM, et al. A multimarker approach to assess the influence of inflammation on the incidence of atrial fibrillation in women. *Eur Heart J*. 2010;31:1730-1736.
22. Jesel L, Arentz T, Herrera-Siklody C, et al. Do atrial differences in endothelial damage, leukocyte and platelet activation, or tissue factor activity contribute to chamber-specific thrombogenic status in patients with atrial fibrillation?. *J Cardiovasc Electrophysiol*. 2014;25:266-270.
23. Akar JG, Jeske W, Wilber DJ. Acute onset human atrial fibrillation is associated with local cardiac platelet activation and endothelial dysfunction. *J Am Coll Cardiol*. 2008;51:1790-1793.
24. Pathak RK, Mahajan R, Lau DH, Sanders P. The implications of obesity for cardiac arrhythmia mechanisms and management. *Can J Cardiol*. 2015;31:203-210.
25. Abed HS, Samuel CS, Lau DH, et al. Obesity results in progressive atrial structural and electrical remodeling: implications for atrial fibrillation. *Heart Rhythm*. 2013;10:90-100.
26. Steffel J, Luscher TF, Tanner FC. Tissue factor in cardiovascular diseases: molecular mechanisms and clinical implications. *Circulation*. 2006;113:722-731.
27. Spronk HM, De Jong AM, Verheule S, et. al. Hypercoagulability causes atrial fibrosis and promotes atrial fibrillation. *Eur Heart J*. 2017;38:38-50.
28. Olesen JB, Torp-Pedersen C, Hansen ML, Lip GY. The value of the CHA2DS2-VASc score for refining stroke risk stratification in patients with atrial fibrillation with a CHADS2 score 0-1: a nationwide cohort study. *Thromb Haemost*. 2012;107:1172-1179.
29. Hirsh BJ, Copeland-Halperin RS, Halperin JL. Fibrotic atrial cardiomyopathy, atrial fibrillation, and thromboembolism: mechanistic links and clinical inferences. *J Am Coll Cardiol*. 2015;65:2239-2251.