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STUDY DESIGN

CARDIOLOGY // ELECTROPHYSIOLOGY

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.[1] 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.[2,3]

The initiation of AF requires a "trigger", which most frequently originates from the pulmonary veins (PV).[4,5] AF begins with paroxysmal episodes that

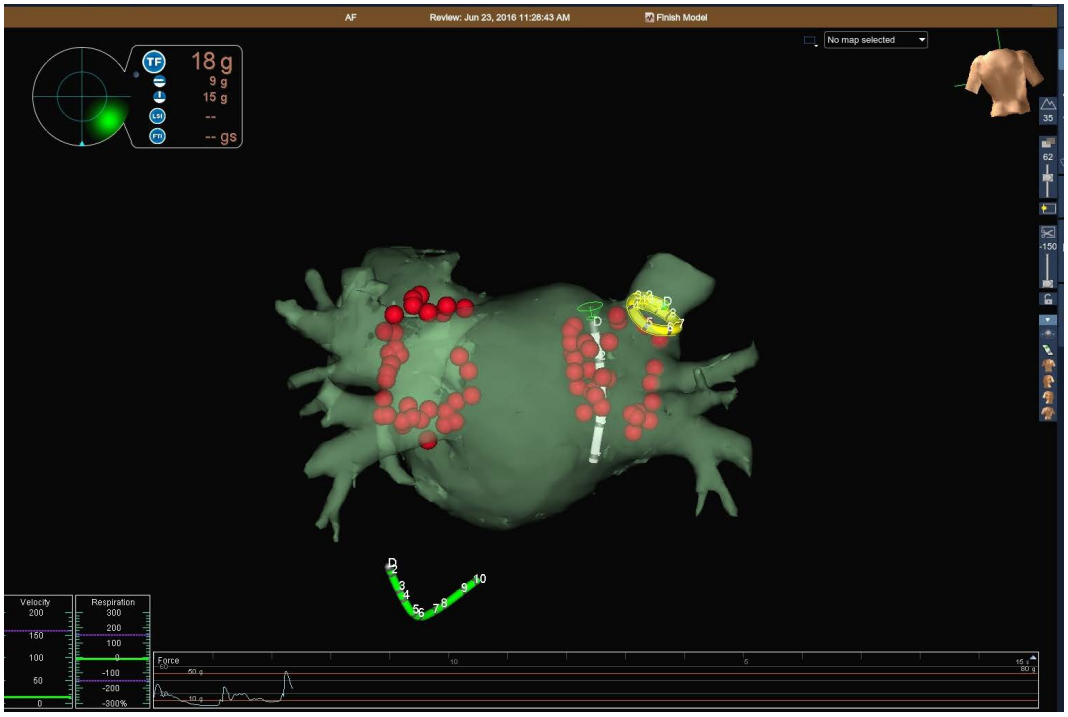

FIGURE 1. Postero-anterior view of the left atrium during the AF ablation. The red tags represent ablation points around the right and left pulmonary veins' ostia. The yellow catheter is the Lasso catheter, which is positioned inside the right superior pulmonary vein. The white catheter is the ablation 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.[6]

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 transseptal approach (Figure 1).[7]

Despite advanced medical technology, the success rate of AF ablation is only 70% in patients with paroxysmal AF and 50% in persistent AF.[8,9] 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.[10–21]

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.[17,22–25]

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.[26–32] EAT is located around the heart, without any barriers between the myocardium of the atria and the ventricle.[33] Inflammatory mediators and adipokines such as high-sensitivity C-reactive protein (hs-CRP), IL-6, IL-8, IL-1b, and TNF-a, 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.[34–43] Furthermore, there is a strong connection between AF, left ventricular diastolic dysfunction, and elevated levels of NT-pro-BNP.[44–48] 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.[49,50]

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.

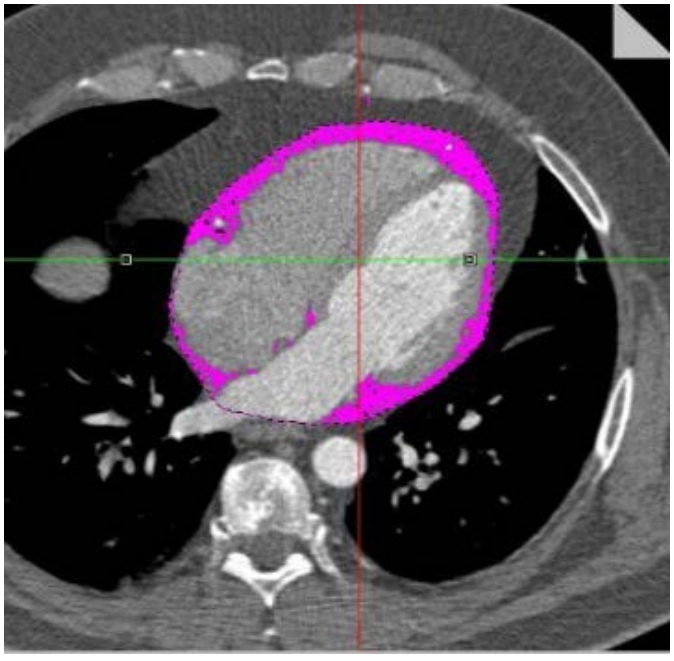

FIGURE 2. Epicardial adipose tissue quantification using native CT

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,

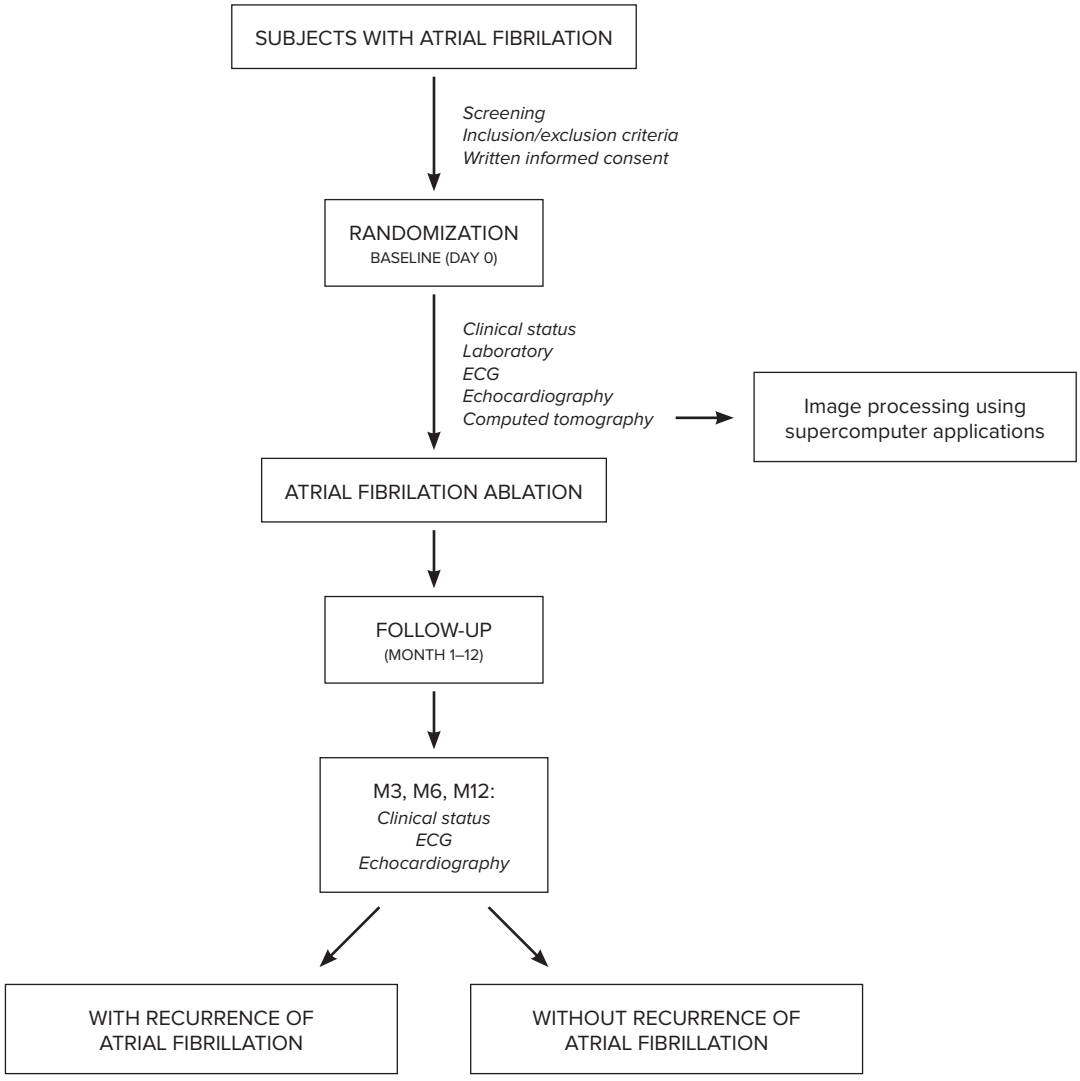

FIGURE 3. INFLAMAP study design

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 Tîrgu Mureș, Romania and of the University of Medicine and Pharmacy of Tîrgu 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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REFERENCES

1. Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation*. 2006:114:e257-e354.
2. Lip GY, Brechin CM, Lane DA. The global burden of atrial fibrillation and stroke: a systematic review of the epidemiology of atrial fibrillation in regions outside North America and Europe. *Chest*. 2012;142:1489-1498.
3. Schnabel RB, Sullivan LM, Levy D, et al. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. *Lancet*. 2009;373:739-745.
4. Haïssaguerre M, Jais P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med*. 1998;339:659-666.
5. Benedek I, Hintea T, Toganel R. Myocardial fibers in pulmonary veins – possible compensatory factor in dilated cardiomyopathy. *Romanian Journal of Internal Medicine*. 1998;36:175-183.
6. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. *Circulation*. 1995;92:1954-1968.
7. Paulus K, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37:2893-2962.
8. Ganesan AN, Shipp NJ, Brooks AG, et al. Long-term outcomes of catheter ablation of atrial fibrillation: a systematic review and meta-analysis. *J Am Heart Assoc*. 2013;2:e004549.
9. Calkins H, Reynolds MR, Spector P, et al. Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: two systematic literature reviews and meta-analyses. *Circ Arrhythm Electrophysiol*. 2009;2:349-361.
10. Kenchaiah S, Evans JC, Levy D, et al. Obesity and the risk of heart failure. *N Engl J Med*. 2002:347:305-313.
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. Dzeshka MS, Lip GY, Snezhitskiy V, Shantsila E4. Cardiac Fibrosis in Patients With Atrial Fibrillation. *JACC*. 2015;66:943-959.
14. Pinto T, Oliveira M, Ramos R, et al. Left atrial appendage volume as a new predictor of atrial fibrillation recurrence after catheter ablation. *J Interv Card Electrophysiol*. 2017;49:165-171.
15. Luong C, Thompson DJ, Bennett M, et al. Right Atrial Volume Is Superior to Left Atrial Volume for Prediction of Atrial Fibrillation Recurrence After Direct Current Cardioversion. *Can J Cardiol*. 2015;31:29-35.
16. Njoku A, Kannabhiran M, Arora R, et al. Left atrial volume predicts atrial fibrillation recurrence after radiofrequency ablation: a meta-analysis. *Europace*. 2018;20:33-42.
17. Tong L, Guangping L, Lijian L, Korantzopoulos P. Association Between C-Reactive Protein and Recurrence of Atrial Fibrillation After Successful Electrical Cardioversion. *J Am Coll Cardiol*. 2007;49:1642-1648.
18. den Uijl DW, Delgado V, Tops LF, et al. Natriuretic peptide levels predict recurrence of atrial fibrillation after radiofrequency catheter ablation. *Am Heart J*. 2011;161:197-203.
19. Xiangdong X, Yongqing T. Relationship between Brain Natriuretic Peptide and Recurrence of Atrial Fibrillation after Successful Electrical Cardioversion: an Updated Meta-Analysis. *Braz J Cardiovasc Surg*. 2017;32:530-535.
20. Therkelsen SK, Groenning BA, Svendsen JH, Jensen GB. Atrial and ventricular volume and function evaluated by magnetic resonance imaging in patients with persistent atrial fibrillation before and after cardioversion. *Am J Cardiol*. 2006;97:1213-1219.
21. Marchese P, Bursi F, Delle Donne G, et al. Indexed left atrial volume predicts the recurrence of non-valvular atrial fibrillation after successful cardioversion. *Eur J Echocardiogr*. 2011;12:214-221.
22. Marchese P, Malavasi V, Rossi L, et al. Indexed left atrial volume is superior to left atrial diameter in predicting nonvalvular atrial fibrillation recurrence after successful cardioversion: a prospective study. *Echocardiography*. 2012;29:276-284.
23. D'Ascenzo F, Corleto A, Biondi-Zoccai G, et al. Which are the most reliable predictors of recurrence of atrial fibrillation after transcatheter ablation?: a meta-analysis. *Int J Cardiol*. 2013;167:1984-1999.
24. Wang TJ, Parise H, Levy D, et al. Obesity and the risk of new-onset atrial fibrillation. *JAMA*. 2004:292:2471-2477.
25. Wanahita N, Messerli FH, Bangalore S, Gami AS, Somers VK, Steinberg JS. Atrial fibrillation and obesity – results of a meta-analysis. *Am Heart J*. 2008:155:310-315.
26. Thanassoulis G, Massaro JM, O'Donnell CJ, et al. Pericardial fat is associated with prevalent atrial fibrillation: the Framingham Heart Study. *Circ Arrhythm Electrophysiol*. 2010;3:345-350.
27. Gaeta M, Bandera F, Tassinari F, et al. Is epicardial fat depot associated with atrial fibrillation? A systematic review and meta-analysis. *Europace*. 2017;19:747-752.
28. Al-Rawahi M, Proietti R, Thanassoulis G. Pericardial fat and atrial fibrillation: Epidemiology, mechanisms, and interventions. *Int J Cardiol*. 2015;195:98-103.
29. Batal O, Schoenhagen P, Shao M, et al. Left atrial epicardial adiposity and atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2010;3:230-236.
30. Greif M, von Ziegler F, Wakili R, et al. Increased pericardial adipose tissue is correlated with atrial fibrillation and left atrial dilatation. *Clin Res Cardiol*. 2013;102:555–562.
31. Chekakie MO, Akar JG. Epicardial Fat and Atrial Fibrillation: A Review. *J Atr Fibrillation*. 2012;4:483.
32. Chekakie MO, Welles CC, Metoyer R, et al. Pericardial fat is independently associated with human atrial fibrillation. *J Am Coll Cardiol*. 2010;56:784-788.
33. Iacobellis G, Corradi D, Sharma AM. Epicardial adipose tissue: anatomic, biomolecular and clinical relationships with the heart. *Nat Clin Pract Cardiovasc Med*. 2005;2:536-543.
34. Sawaya SE, Rajawat YS, Rami TG, et al. Downregulation of connexin40 and increased prevalence of atrial arrhythmias in transgenic mice with cardiac-restricted overexpression of tumor necrosis factor. *Am J Physiol Heart Circ Physiol*. 2007;292:H1561-H1567.
35. Marcus GM, Whooley MA, Glidden DV, Pawlikowska L, Zaroff JG, Olgin JE. Interleukin-6 and atrial fibrillation in patients with coronary artery disease: data from the Heart and Soul Study. *Am Heart J*. 2008;155:303-309.
36. Tselentakis EV, Woodford E, Chandy J, Gaudette GR, Saltman AE. Inflammation effects on the electrical properties of atrial tissue and inducibility of postoperative atrial fibrillation. *J Surg Res*. 2006;135:68-75.
37. 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.
38. Malouf JF, Kanagala R, Al Atawi FO, et al. High sensitivity C-reactive protein: a novel predictor for recurrence of atrial fibrillation after successful cardioversion. *J Am Coll Cardiol*. 2005;46:1284-1287.
39. Aviles RJ, Martin DO, Apperson-Hansen C, et al. Inflammation as a risk factor for atrial fibrillation. *Circulation*. 2003;108:3006-3010.

40. Rotter M, Jais P, Vergnes MC, et al. Decline in C-reactive protein after successful ablation of long-lasting persistent atrial fibrillation. *J Am Coll Cardiol*. 2006;47:1231-1233.
41. Sacks HS, Fain JN. Human epicardial adipose tissue: a review. *Am Heart J*. 2007;153:907-917.
42. Verheule S, Sato T, Everett TT, et al. Increased vulnerability to atrial fibrillation in transgenic mice with selective atrial fibrosis caused by overexpression of TGF-beta1. *Circ Res*. 2004;94:1458-1465.
43. Konishi M, Sugiyama S, Sugamura K, et al. Accumulation of pericardial fat correlates with left ventricular diastolic dysfunction in patients with normal ejection fraction. *J Cardiol*. 2012;59:344-351.
44. Palazzuoli A, Beltrami M, Ruocco G, et al. The Role of Natriuretic Peptides for the Diagnosis of Left Ventricular Dysfunction. *Scientific World Journal*. 2013;2013:784670.
45. Mottram PM, Leano R, Marwick TH. Usefulness of B-type natriuretic peptide in hypertensive patients with exertional dyspnea and normal left ventricular ejection fraction and correlation with new echocardiographic indexes of systolic and diastolic function. *Am J Cardiol*. 2003;92:1434-1438.
46. Lubien E, DeMaria A, Krishnaswamy P, et al. Utility of B-natriuretic peptide in detecting diastolic dysfunction: comparison with Doppler velocity recordings. *Circulation*. 2002;105:595-601.
47. Ellinor PT, Low AF, Patton KK, Shea MA, Macrae CA. Discordant atrial natriuretic peptide and brain natriuretic peptide levels in lone atrial fibrillation. *J Am Coll Cardiol*. 2005;45:82-86.
48. Wozakowska-Kaplon, B. Effect of sinus rhythm restoration on plasma brain natriuretic peptide in patients with atrial fibrillation. *Am J Cardiol*. 2004;93:1555-1558.
49. Bartkowiak, R, Wozakowska-Kapłon B, Janiszewska G. Plasma NT-proANP in patients with persistent atrial fibrillation who underwent successful cardioversion. *Kardiol Pol*. 2012;68:48-54.
50. Yamada T, Murakami Y, Okada T, et al. Plasma atrial natriuretic peptide and brain natriuretic peptide levels after radiofrequency catheter ablation of atrial fibrillation. *Am J Cardiol*. 2006;97:1741-1744.