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RESEARCH ARTICLE

IS SMOKING EFFECTIVE ON RECURRENCE AFTER ATRIAL FIBRILLATION ABLATION THERAPY?

Esra Dugral[1], Oguzhan Ekrem Turan[2], Ahmet Anıl Baskurt[2], Emin Evren Ozcan[2]

[1] Dokuz Eylul University, Institute of Health Sciences, Pulmonology/Physiology, Izmir, Turkey
[2] Dokuz Eylul University, Department of Internal Medicine, Department of Cardiology, Izmir, Turkey

Corresponding Author: Esra Dugral, MD, **E-mail:** srbilgin@gmail.com
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ABSTRACT

Purpose: To investigate the recurrence rates after Atrial Fibrillation ablation therapy in smokers compared to nonsmokers.

Method: Patients who underwent Pulmonary Vein Isolation (PVI) ablation for symptomatic AF unresponsive to medical therapy between January 2016 and June 2018 were included in the study. Demographic data and smoking were obtained from medical records registered in the hospital database. For PVI, RF ablation with 3D mapping or Cryobalon ablation was performed according to operator preference. A 12-lead surface electrocardiogram and 24-hour ambulatory Holter electrocardiogram were performed at 1 and 3 months after the procedure and every 3 months thereafter. A 3-month blind period was used when evaluating AF recurrences. Atrial tachycardia and atrial flutter, which were found to have just started after ablation, were also considered as recurrence.

Results:139 patients who underwent AF ablation were included in our study. AF recurrence was observed in 38 (27.3%) of the patients included in the study during a total follow-up period of 37 months. Age, gender, hypertension and diabetes history were similar in both groups (all p values> 0.05). However, smokers were more common in the relapsed group (39.5% vs. 21.8%, p=0.03). Except for 0.3 mg/dl, p=0.04) values, no significant biochemical parameter affecting AF recurrence was detected. As a result of multivariate regression analysis, independent predictors of recurrence after AF ablation were smoking (OR=2.29, 95% CI 1-5.23, p=0.05) and Neutrophil/Lymphocyte Ratio (NLR) over 3 (OR=3.08, 95% CI 1.09). -8.69, p = 0.033).

Conclusion: It was determined that recurrence after AF ablation treatment was higher in smokers compared to non-smokers. Smoking cessation therapy should be considered primarily in order to prevent recurrence in patients receiving AF ablation therapy.

Keywords: Smoking, atrial fibrillation, ablation therapy, recurrens, inflammation

INTRODUCTION

Atrial fibrillation (AF) is the most common supraventricular tachyarrhythmia and is a cardio-pathology that causes hemodynamic deterioration due to the loss of function of the atria as a result of irregular electrical activity. The incidence increases in men and as age progresses. While the incidence is around 1% under the age of 60, this rate rises to 5-

10% in people aged 70 and over (1). An epidemiological study conducted in 2010 showed that there are 33.5 million AF patients worldwide; showed that the incidence rate between the sexes was 0.60% in men and 0.37% in women (2). As an independent risk factor, AF increases all-cause mortality rates 1.5 times in men and 2 times in women (3,4). In addition to increased mortality, increased morbidity and adverse effects on quality of life are common with AF (5). Among the complications of AF; myocardial infarction, heart failure and ischemic stroke are the most important (2).

Cigarette smoking exposes you to more than 4000 substances, especially nicotine and carbon monoxide. While carbon monoxide causes a decrease in tissue oxygenation by competing with the oxygen in hemoglobin, nicotine causes atrial fibrosis with increased sympathetic activity (6). The Copenhagen City Heart Study showed a significant association between reduced lung function and the risk of AF (7). The fact that smoking causes a decrease in lung functions in addition to its negative effects on heart health has made its role in the development of AF clear (7,8). Recent studies have contributed to this situation by estimating the risk of smoking-related AF as 24% (9).

It is known that smoking is effective in chronic diseases such as chronic obstructive pulmonary disease (COPD) and cardiovascular diseases through inflammation (7,10). Studies have proven that smoking increases many inflammatory markers such as C-reactive protein (CRP), Tumor Necrosis Factor alpha (TNF-alpha), and Interleukin-6 (IL-6) (11,12). As a result of exposure to cigarettes, there is an increase in the release of cytokines, and this increase contributes significantly to the increase in the systemic inflammatory response (13,14). Increased inflammation increases fibrosis, leading to structural remodeling of the myocardium, thus increasing the risk of AF (15).

When the literature is examined, it is seen that many studies have been conducted on the relationship between smoking and AF. However, studies on the frequency of recurrence after ablation therapy in patients who smoke and have a diagnosis of AF are limited. In this study, we wanted to examine the relationship between the recurrence rate after AF ablation therapy and smoking.

METHOD

Patient Population

Patients who underwent pulmonary vein isolation ablation for symptomatic AF unresponsive to medical therapy between January 2016 and June 2018 were included in the study. Patients with a previous history of AF ablation were not included in the study. Demographic data and smoking status were obtained from medical records registered in the hospital database. Previous smokers and current smokers were defined as smokers. Classification of AF was made on the basis of the 2017 HRS HRS/EHRA/ECAS/APHRS/SOLAECE expert report as of the time of ablation of the patients included in the study (16). Paroxysmal AF was defined as persistent AF that ended spontaneously in 7 days or less, and persisted over 7 days for less than 1 year.

Electrophysiological Study and Ablation

Written confirmation of the procedure was obtained from the patients. Anticoagulation therapy of the patients was not discontinued, and transesophageal echocardiography showed no atrial thrombus before ablation therapy. For Pulmonary Vein Isolation (PVI), RF ablation with 3D mapping or Cryobalon ablation was performed according to the operator's preference. The patients underwent electrophysiological study and ablation after 8 hours of fasting. A 3D electroanatomical mapping system (CARTO, Biosense Webster, Inc. DiamondBar, CA, USA) was used for RF ablation. Left PVs and then right PVs were isolated with RF energy. After the lines were created, PVI was completed by showing the pulmonary vein entry and exit blocks. Cryobalon ablation was performed using the Arctic Front™ Cardiac Cryoablation Catheter System (Medtronic, USA). A 28 mm second generation cryoballon catheter (Arctic Front Advance, Medtronic Inc, Minneapolis) was used for ablation. It was started with the upper left PV, followed by isolation of the lower left PV, the upper right PV, and the lower right PV, respectively. The duration of each freezing cycle was 240 seconds. Complete isolation was demonstrated again with Achieve mapping catheter after PVI.

Post Ablation Management And Follow-Up

Following ablation therapy, patients were told to

continue with antiarrhythmic drugs and oral anticoagulants prescribed 3 months ago. The patients were followed up in the outpatient clinic at the 1st and 3rd months following the treatment and every 3 months thereafter. The symptoms of the patients were questioned at the controls, and routine 12-lead surface electrocardiogram and 24-hour ambulatory Holter electrocardiogram were performed when deemed necessary after ablation. A 3-month blind period was used when evaluating AF recurrences. Arrhythmic episodes lasting 30 seconds or longer were considered AF recurrence. New onset atrial tachycardia and atrial flutter were also considered as relapses.

Statistical Analysis

SPSS (version 24, IBM corp.) program was used for statistical analysis. Continuous variables were expressed as mean and standard deviation. Categorical variables were expressed as percentages. The fit for normal distribution was evaluated using histogram, plot graphs and kolomogrov smirnov test. The difference between the groups was evaluated with the T-test for continuous variables with normal distribution, and with Mann Withney U test for continuous variables without. Chi-square test was used to determine the differences between groups for categorical variables. P value below 0.05 was considered statistically significant. Possible factors identified by univariate analysis were used to identify predictors of AF recurrence in multivariate analysis. Hosmer-Lemeshow goodness-of-fit statistics were used to evaluate the model fit. A 5% type I error level was used for statistical significance.

Ethical Permission

Ethical approval for the study was obtained from the Non-Interventional Research Ethics Committee of Dokuz Eylul University on 19.04.2021 with the decision number 2021/13-27.

RESULTS

Our study included 139 patients who underwent AF ablation. AF recurrence was observed in 38 (27.3%) of the patients included in the study during a total follow-up period of 37 months (20-48). Demographic data of patients with and without recurrence were similar. Demographic, procedural and echocardiographic data of the groups are given in Table 1. Age, gender, hypertension and diabetes history were similar in both groups (all p values > 0.05). However, smokers were more common in the relapsed group (39.5% vs. 21.8%, p=0.03). Again, the rates of drugs used by the patients ACEinh and beta blockers were similar (p 0.48 and 0.22, respectively). The use of antiarrhythmic drugs (class 1c and amiodarone) that may affect AF recurrence was the same in both groups (23.7% vs. 24.8%, p=0.87 and 28.9% vs. 18.8%, p=0.30). Although the rate of persistent AF was higher in the relapsed group, it did not reach statistical significance (23.8% vs. 40, p=0.07). Three-fourths of the patients underwent ablation with an RF catheter, while one-fourth of them underwent AF ablation with a cryoballon. In our study group, AF recurrence was not associated with the ablation method used (p=0.44). No statistical correlation was found between echocardiographic parameters, LVEF and left atrial diameter, and AF recurrence (p 0.51 and 0.9, respectively). In routine laboratory parameters, no significant biochemical parameter affecting AF recurrence was detected, except Neutrophil Lymphocyte Ratio (NLR) values above 3 (23% vs 8.9%, p=0.02) and albumin (3.9±0.4 vs 4.1±0.3 mg/dl, p=0.04). As a result of multivariate regression analysis, independent predictors of recurrence after AF ablation were smoking (OR=2.29, 95% CI 1-5.23, p = 0.05) and 3 above NLR (OR=3.08, 95% CI 1.09-8.69, p = 0.033).) is that.

DISCUSSION

Today, strategies for cardiac rhythm and rate control are used in the treatment of AF, which causes an increased risk of mortality and morbidity in patients. The most effective treatment method that has proven itself is Pulmonary Vein Isolation (PVI). Although it is the most effective treatment, in the first year there is a 10% recurrence rate after diagnosis and approximately 5% in each subsequent year (17). The development of recurrence in patients undergoing PVI depends on many factors. They are divided into two as changeable and non-changeable factors. While genetic features, advancing age are unchangeable factors, features such as obesity, Obstructive Sleep Apnea Syndrome (OSAS), alcohol consumption, excessive exercise, and smoking are changeable factors. There are no adequate studies on the benefit of medical therapy or re-ablation in patients who develop relapse. Controlling modifiable factors affecting recurrence in this patient group affects the course of AF.

Table 1. Baseline clinical characteristics and echocardiographic data of the study population

Variables	Recurrent (n=38)	Non-recurrent (n=101)	p value
Age (year)	57.7±12.5	56.8±10.5	0.65
Female Gender, N (%)	22 (57.9)	46 (45.5)	0.19
HT, n (%)	17 (44.7)	48 (47.5)	0.81
DM, n (%)	7 (18.4)	13 (12.9)	0.38
Smoking, n (%)	15 (39.5)	22 (21.8)	0.03
ACE inh., n (%)	12 (31.6)	38 (37.6)	0.48
B blocker, n (%)	25 (65.8)	55 (54.4)	0.22
Class 1c antiarrhythmic, n (%)	9 (23.7)	25 (24.8)	0.87
Amiodarone, n (%)	11 (28.9)	19 (18.8)	0.30
PAF, n (%)	26 (23.8)	83 (76.2)	0.07
Persistant AF, n (%)	12 (40)	18 (60)	0.07
Cryoablation, n (%)	12 (23.5)	39 (76.5)	0.44
RF ablation, n (%)	26 (26.2)	62 (73.8)	0.44
LVEF (%)	57.3±4.6	58.2±4.4	0.50
LA, cm	5±0.6	4.9±0.6	0.91

HT: Hipertension, DM: Diabetes mellitus, PAF: Paroxysmal Atrial Fibrillation, AF: Atrial Fibrillation, ACE: Angiotensin Converting Enzyme, LVEF: Left Ventricular Ejection Fraction, LA: Left Atrium

Although the ablation procedure preferred for the treatment of AF is successful, the possibility of recurrence exists. Recurrence types seen after ablation are examined in 3 groups according to the time period they occurRelapses seen within the first 3 months after ablation therapy are called early recurrence, those seen between 3 months and 1 year are called late recurrence, and those seen after 1 year are called very late recurrence. Studies have shown that early recurrence is seen in 50% and more of the patients. Tissue inflammation response after ablation and the emergence of transient stimulatory areas were thought to be the cause of this recurrence. About half of patients with early recurrence show improvement after follow-up. Late relapse is seen in 25-40% of patients. Studies have shown that late recurrence may be due to recovery of electrical conduction. Very late recurrences were mostly attributed to reasons such as the re-activation of stimuli in and around the pulmonary vein (PV), and the development of triggers other than PV. It has been reported that it is mostly seen in elderly and obese patients with underlying heart disease (16).

139 patients included in our study were followed for 48 months and AF recurrence was observed in 38 (27.3%) of them. When the demographic data of the patients such as age and gender, rates of underlying disease (Hypertension (HT), Diabetes Mellitus (DM)), drug use (antiarrhythmics that may affect AF recurrence, ACE inh, beta blockers) were examined, no significant difference was found between the groups with and without recurrence. Although the rate of persistent AF was higher in the relapsed group, it was not statistically significant. When we look at the treatment methods, three-quarters of the patients were ablated with an RF catheter (n:88; Recurrence n:26 Non-Recurrence n:62), and AF ablation treatment with cryoballon (n:51; Recurrence n:12, Non-Recurrence n: 39) seems to have been implemented. In the statistical study, it was shown that AF ablation treatment method was not associated with AF recurrence (p=0.44). When echocardiographic findings were examined, no statistically significant difference was found between AF recurrence and LVEF and left atrial diameter (p= 0.51 and 0.9, respectively) (Table 1) although both group had enlarged left atrial diameter.

When we look at the causes that increase the risk of AF, it is seen that there are physiological changes such as advanced age, male gender, obesity and alcohol consumption, as well as underlying diseases such as chronic heart diseases, diabetes, and hypertension, and habits that reduce the quality of life (18). Smoking, one of these habits, has been shown to be an independent risk factor for AF in studies. Although there is a dose-response relationship between smoking and AF this relationship is not completely linear (19,20). The Rotterdam Study, one

Table 2. Biochemical data of patient groups

Variables	Recurrent (n=38)	Non-recurrent (n=101)	p value
Glucose, mg/dl	94.3±12.7	102.1±35.7	0.25
Creatinin, mg/dl	0.8±0.2	0.92±0.09	0.45
Sodium, mmol/L	140.2±1.9	138.7±1.3	0.50
Potassium, mmol/L	4.2±0.4	4.3±0.4	0.67
AST, U/L	25.4±9.5	27.1±16.9	0.56
ALT, U/L	24.6±12.5	26.5±13.9	0.69
WBC, 10*3/uL	7.4±2.2	7.3±1.9	0.69
Hb, g/dl	13.3±1.9	13.8±1.5	0.23
Htc, %	40±5.4	41.2±4.3	0.22
Plt, 10*3/uL	215.9±66.6	227.9±61.4	0.41
Neutrophil, 10*3/uL	4.6±1.8	4.2±1.5	0.18
Lymphocyte, 10*3/uL	2.2±0.7	2.2±0.7	0.99
NLR	2.3±1.2	2±1.1	0.24
NLR ≥3, n (%)	9 (23.7)	9 (8.9)	0.02
CRP, mg/L	4.4±3.8	3.6±4.2	0.54
Albumin	3.9±0.4	4.1±0.3	0.04
CRP albumin ratio	1.3±0.9	0.9±1.1	0.23

of the most important prospective cohort studies on this subject, showed that the risk of AF increased equally when former smokers and active smokers were compared (21). In the ARIC (Atherosclerosis Risk in Communities Study), the incidence of AF was found to increase 2 times in active smokers and 1.58 times in people who were smokers (active smokers + former smokers) compared to those who had never smoked. It has also been shown that the risk of AF is reduced in former smokers and ex-smokers (22).

One of the reasons why smoking increases the incidence of AF is the increase in sympathetic activation and the resulting cardiac workload (7). Vasoconstriction occurs with sympathetic activity and increases heart rate. The carbon monoxide in the cigarette competes with the oxygen molecule attached to the hemoglobin, causing deterioration in the oxygen carrying capacity of the hemoglobin. Deterioration of oxygen transported to tissues and increased cardiac workload cause both cardiac muscle hypertrophy and myocardial ischemia (23). Smoking causes a decrease in oxygen transport to the tissues, causing oxidative stress in the tissues, along with deterioration in the vessel wall and vasomotor dysfunction. The effects of smoking on lipid peroxidation metabolism and the association of endothelial dysfunction also lead to atherosclerosis (24). COPD formation, one of the best known and most studied effects of smoking, also causes right heart failure and a decrease in atrial functions (7). As a result, it has been shown that smoking increases the cardiac workload, affects atrial ischemia by causing atreosclerosis, increases atrial fibrosis, causes right heart failure by impairing lung functions, and all these effects increase the risk of AF (19,20). Studies have shown that nicotine dose-dependently induces collagen III mRNA expression causing atrial fibrosis and this structural change prepares the ground for AF by slowing down the electrical impulse transmission in the heart tissue (7). Evidence has been presented in animal experiments that increased nicotine associated with smoking increases the risk of AF by increasing interstitial fibrosis. (26). Atrial fibrosis increases the incidence of atrial arrhythmias by providing an arrhythmogenic environment (19).

In our study, the files of the patients who applied to Dokuz Eylul University Cardiology Department Arrhythmia Clinic due to cardiac arrhythmia were analyzed retrospectively and it was recorded whether they smoked or not. Studies have shown that people who have smoked at some point in their lives (active smokers + ex-smokers) have a greater increased risk of AF compared to people who have never smoked (21). Based on these studies, current or former smokers were included in the group of smokers. In

our study, recurrence rates were found to be statistically significantly higher in the smokers group than in the non-smokers (39.5% vs. 21.8%, p=0.03). This result is quite significant and compatible with the literature.

One of the causes of AF is inflammation, and studies have shown that tissue samples taken from the atria of patients with AF have more inflammatory cells compared to the control group (27,28). In another remarkable prospective study, it was shown that after an 8-year follow-up, a higher rate of AF developed in patients with high CRP levels (29). It has been shown that not only CRP, but also other inflammatory markers such as TNF (Tumor Necrosis Factor), IL (interleukin)-1, IL-6, increase the risk of AF (30-32). Inflammatory markers are used in the diagnosis of diseases with inflammation in their etiology and in the follow-up of their treatments. Among them, the neutrophil/lymphocyte ratio (NLR) is frequently used today as a cheap, easy to calculate, reliable and sensitive marker of inflammation. It is accepted between 1.00-2.30. As the inflammation worsens, the NLR value also increases. While the NLR value is 2.4-2.99 in subclinical inflammation, the NLR value is between 3.0-6.99 in low-grade inflammation. NLR values increase as the intensity of inflammation increases. In severe sepsis and post-chemotherapy patients, low NLR values(< 0.7) are present and are associated with the severity of inflammation (33). In our study, in the group of patients with a Neutrophil Lymphocyte Ratio (NLR) ≥3 who had recurrence after AF ablation therapy found to be significantly higher. (Table 2) (p=0.02). It is known that smoking causes an increase in many inflammatory markers such as CRP, TNF alpha, IL-6 in both men and women (7,34). Therefore, the increase in inflammation with smoking which is considered a predisposing factor for AF, coincides with the high recurrence rate after ablation in smokers and patients with NLR ≥3 in our study.

The decrease in serum albumin level occurs in response to inflammation and adversely affects cardiovascular health by causing increased platelet functions and impaired endothelial function. The reduction of albumin in the presence of inflammation has led to its acceptance as a negative acute phase reactant (35,36). A prospective cohort study showing that low albumin in the first 48 hours of intensive care patients is associated with newly detected AF and recurrent episodes of AF revealed that low albumin levels are important in AF (37). In addition, it has been shown that hypoalbuminemia is effective in the occurrence of myocardial infarction and the increase in related mortality (38). In our study, we found significantly lower albumin levels in patients with recurrence compared to patients without recurrence (3.9±0.4 and 4.1±0.3, respectively, p:0.04). This result shows that our study is compatible with the literature.

CRP is frequently used as an inflammatory marker and is released from the liver. Recently, studies have been conducted showing that the CRP/Alb parameter obtained by proportioning the positive acute phase reactant CRP with the negative acute phase reactant albumin is associated with mortality (39,40). It is thought that the inflammation is more severe in patients with a high CRP/albumin ratio and shows a poor prognosis in patients in acute critical condition and patients with malignancy (41-43). In addition, CRP/Alb ratio has been shown to be superior in determining inflammation with CRP and albumin alone (44). In our study, CRP level and CRP/Alb ratio were found to be high in patients with relapse, but the difference was not significant when compared with patients without recurrence. We think that the difference can be revealed by a study with wider participation.

In conclusion; In our study, it was shown that smoking significantly increased the recurrence rates after AF ablation therapy. In addition, the higher rate of NLR used as an inflammatory marker in the relapsed group and the lower levels of albumin, a negative acute phase reactant, revealed the importance of inflammation in relapse cases. Considering the contribution of smoking to the increase of inflammation, it is important to give priority to smoking cessation treatment in the treatment of AF patients.

Study Limitations

The study was conducted among patients admitted to a single arrhythmia center, which limits its generalizability. More accurate results will be obtained in multi-centre participations. Another limitation of our study is that the parameters such as obesity, alcohol use, physical exercise, obstructive sleep apnea syndrome and structural heart disease among the included patient groups were not adequately examined. We think that multicenter and wider participation studies will provide a valuable contribution to the literature.

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REFERENCES

1. Heeringa J, van der Kuip DAM, Hofman A, et al., Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. Eur Heart J, 2006;27(8):949-53.
2. Chugh, S. S., Havmoeller, R., Narayanan, K. Et al, Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation, 2014;129(8):837-47.
3. January CT, Wann S, Alpert JS, et al, 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society, Circulation, 2014;130(23):2071-104.
4. Anderson JL, Halperin JL, Albert NM, Bozkurt B, et al., Management of patients with atrial fibrillation (compilation of 2006 ACCF/AHA/ESC and 2011 ACCF/AHA/HRS recommendations): a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, J Am Coll Cardiol, 2013;61(18):1935-44.
5. Gronefeld GC, Lilienthal J, Kuck KH, Hohnloser SH; Impact of rate versus rhythm control on quality of life in patients with persistent atrial fibrillation. Results from a prospective randomized study. Eur Heart J, 2003;24(15):1430-6.
6. Goette A, Lendeckel U, Kuchenbecker A, et al., Cigarette smoking induces atrial fibrosis in humans via nicotine. Heart 2007;93(9): 1056–63.
7. Buch P, Friberg J, Scharling H, Lange P, Prescott E, Reduced lung function and risk of atrial fibrillation in the Copenhagen City Heart Study. Eur Respir J., 2003;21(6):1012-6.
8. Ambrose JA, Barua RS., The pathophysiology of cigarette smoking and Cardiovascular disease: anupdate. J Am Coll Cardiol., 2004;43(10):1731-7.
9. Wang Q, Gou Y, Wu C, et al. Smoking as a Risk Factor for the Occurrence of Atrial Fibrillation in Men Versus Women: A Meta-Analysis of Prospective Cohort Studies. Heart Lung Circ., 2018;27(1):58-65.
10. Tibuakuu M, Kamimura D, Kianoush S, et al., The association between cigarette smoking and inflammation: The Genetic Epidemiology Network of Arteriopathy (GENOA) study. PLoS One., 2017 Sep 18;12(9):e0184914.
11. Mendall MA, Patel P, Asante M, et al. Relation of serum cytokine concentrations to cardiovascular risk factors and coronary heart disease. Heart.,1997;78(3):273-7.
12. Tappia PS, Troughton KL, Langley-Evans SC, Grimble RF., Cigarette smoking influences cytokine production and antioxidant defenses. Clin Sci (Lond)., 1995;88(4):485-9.
13. Goncalves RB, Coletta RD, Silverio KG, et al., Impact of smoking on inflammation: overview of molecular mechanisms. Inflamm Res., 2011;60(5):409-24.
14. Rom O, Avezov K, Aizenbud D, Reznick AZ., Cigarette smoking and inflammation revisited. Respir Physiol Neurobiol., 2013;187(1):5-10.
15. D'Alessandro A, Boeckelmann I, Hammwhoner M, Goette A, Nicotine, cigarettes moking and cardiac arrhythmia: an overview. Eur J Prev Cardiol., 2012;19(3):297-305.
16. Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Europace., 2018;20(1):e1-e160.
17. Kirchhof P, Bax J, Blomstrom-Lundquist C, et al., Early and comprehensive management of atrial fibrillation: executive summary of the proceedings from the 2nd AFNET-EHRA consensus conference 'research perspectives in AF', Eur Heart J., 2009;30(24):2969-77c.
18. Andrade J, Khairy P, Dobrev D, Nattel S, The Clinical Profile and Pathophysiology of Atrial Fibrillation Relationships Among Clinical Features, Epidemiology, and Mechanisms, Circ Res., 2014;114(9):1453-68.
19. Staerk L, Sherer J A, Ko D, Benjamin E J, Helm RH, Atrial Fibrillation: Epidemiology,

Pathophysiology, and Clinical Outcomes, Circ Res., 2017;120(9):1501-1517.
20. Alonso A, Krijthe BP, Aspelund T, et al. Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium., J Am Heart Assoc., 2013;2(2):e000102.
21. Heeringa J, Kors JA, Hofman A, van Rooij FJ, Witteman JC. Cigarette smoking and risk of atrial fibrillation: the Rotterdam Study. Am Heart J., 2008;156(6):1163-9.
22. Chamberlain AM, Agarwal SK, Folsom AR, et al. Smoking and incidence of atrial fibrillation: results from the Atherosclerosis Risk in Communities (ARIC) study. Heart Rhythm., 2011;8(8):1160-6.
23. Moliterno DJ, Willard JE, Lange RA, et al., Coronary-artery vasoconstriction induced by cocaine, cigarette smoking, or both. N Engl J Med., 1994;330(7):454-9.
24. Levitzky YS, Guo CY, Rong J, et al, Relation of smoking status to a panel of inflammatory markers: the framingham offspring. Atherosclerosis., 2008;201(1):217-24.
25. Shan H, Zhang Y, Lu Y, et al., Downregulation of miR-133 and miR-590 contributes to nicotine-induced atrial remodelling in canines. Cardiovasc Res., 2009;83(3):465-72.
26. Frustaci A, Chimenti C, Bellocci F, Morgante E, Russo MA, Maseri A. Histological substrate of atrial biopsies in patients with lone atrial fibrillation. Circulation., 1997;96(4):1180-4.
27. Nakamura Y, Nakamura K, Fukushima-Kusano K, et all. Tissue factor expression in atrial endothelium associated with nonvalvular atrial fibrillation: possible involvement in intracardiac thrombogenesis. Thromb Res., 2003;111(3):137-42.
28. Aviles RJ, Martin DO, Apperson-Hansen C, et al., Inflammation as a risk factor for atrial fibrillation. Circulation. 2003;108(24):3006-10.
29. Boos CJ, Anderson RA, Lip GY. Is atrial fibrillation an inflammatory disorder? Eur Heart J. 2006;27(2):136-49.
30. Asselbergs FW, van den Berg MP, Diercks GF, van Gilst WH, van Veldhuisen DJ. Creactive protein and microalbuminuria are associated with atrial fibrillation. Int J Cardiol., 2005;98(1):73-7.
31. Psychari SN, Apostolou TS, Sinos L, Hamodraka E, Liakos G, Kremastinos DT. Relation of elevated C-reactive protein and interleukin-6 levels to left atrial size and duration of episodes in patients with atrial fibrillation. Am J Cardiol., 2005;95(6):764-7.
32. Zahorec R., Neutrophil-to-lymphocyte ratio. Sixteen-year-long history since publication of our article in Bratislava Medical Journal, Bratisl Lek Listy. 2017;118(6):321-323.
33. Bermudez EA, Rifai N, Buring JE, Manson JE, Ridker PM. Relation between markers of systemic vascular inflammation and smoking in women. Am J Cardiol. 2002;89(9):1117-9.
34. Wada H, Dohi T, Miyauchi K, et al. Independent and combined effects of serum albumin and C-reactive protein on longterm outcomes of patients undergoing percutaneous coronary intervention. Circ J. 2017;81(9):1293-1300.
35. Joles JA, Willekes-Koolschijn N, Koomans HA. Hypoalbuminemia causes high blood viscosity by increasing red cell lysophosphatidylcholine. Kidney Int. 1997;52(3):761-70.
36. Van Beek DEC, Kuijpers YAM, Königs MHH, van der Horst ICC, Scheeren TWL., Low serum albumin levels and new-onset atrial fibrillation in the ICU: a prospective cohort study. J Crit Care. 2020;56:26-30.
37. Nelson JJ, Liao D, Sharrett AR, et al. Serum albümin level as a predictor of incident coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) study. Am J Epidemiol. 2000;151(5):468-77.
38. Yu ST, Zhou Z, Cai Q, et al. Prognostic value of the C-reactive protein/albumin ratio in patients with laryngeal squamous cell carcinoma. Onco Targets Ther. 2017;10:879-884.
39. Liu Z, Jin K, Guo M, et al. Prognostic value of the CRP/Alb ratio, a novel inflammation-based score in pancreatic cancer. Ann Surg Oncol. 2017;24(2):561-568.
40. Fairclough E, Cairns E, Hamilton J, Kelly C., Evaluation of a modified early warning system for acute medical admissions and comparison with C reactive protein/albumin ratio as a predictor of patient outcome. Clin Med (Lond). 2009;9(1):30-3.
41. Ranzani OT, Zampieri FG, Forte DN, Azevedo LC, Park M., C-Reactive Protein/Albumin Ratio Predicts 90-Day Mortality of Septic Patients. PLoS One. 2013;8(3):e59321.,
42. Kinoshita A, Onoda H, Imai N, et al. The C-reactive protein/albümin ratio, a novel inflammation-based prognostic score, predicts

outcomes in patients with hepatocellular carcinoma. Ann Surg Oncol. 2015;22(3):803-10.
43. Kalyoncuoglu M, Durmus G. Relationship between C-reactive protein-to-albumin ratio and the extent of coronary artery disease in patients with non-ST-elevated myocardial infarction. Coron Artery Dis. 2020;31(2):130-136.