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RISK FACTORS OF ATRIAL FIBRILLATION AND THEIR MODIFICATION: A NEW LOOK AT A LONG-TERM PROBLEM

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Abstract. Risk factors of atrial fibrillation and their modification: a new look at a long-term problem. Babkina T.M., Smyrnova H.S., Hladka L.Yu., Polishchuk O.V. Atrial fibrillation (AF) is one of the most common arrhythmias diagnosed in clinical practice. Today, AF is associated with an increased risk of mortality, acute brain disorders, and heart failure. The results of many studies suggest that the incidence of AF is directly related to such risk factors (RF) as age, obesity, hypertension, diabetes mellitus, obstructive sleep apnea, alcohol, tobacco smoking etc. Recently published studies have described the positive impact of lifestyle changes on the incidence of AF. Therefore, it is believed that early detection of RF could prevent or delay the onset of AF. New data suggest the need to review the management of patients with AF. In 2020, the American Heart Association has presented a scientific statement that highlighted the relationship between modified RF and AF, discussed the implementation of strategies for effective modification of RF, as well as identified areas for new research. The data allow us to conclude that the correction of RF helps to reduce the incidence of AF. Future research is needed to establish the effects and generalizability of systematic lifestyle and RF modification for AF: to study the role of pericardial/epicardial fat accumulation in risk and progression of AF; determination of the most effective weight loss techniques for long-term success in reducing AF; effects of high-intensity/short-duration interval training on left atrium structural and electric remodeling; the degree of glycemic control for AF.

Реферат. Факторы риска фибрилляции предсердий и их модификация: новый взгляд на многолетнюю проблему. Бабкина Т.М., Смирнова А.С., Гладкая Л.Ю., Полищук Е.В. Фибрилляция предсердий (ФП) является одной из наиболее распространенных аритмий, которые диагностируют в клинической практике. На сегодня ФП является угрозой для здоровья, которая постоянно растет и ассоциируется с увеличением риска смертности, острых мозговых нарушений и сердечной недостаточности. Результаты многих исследований указывают на то, что заболеваемость ФП связана с такими факторами риска (ФР), как пожилой возраст, ожирение, гипертония, сахарный диабет, синдром обструктивного апноэ сна, употребление алкоголя, табака и др. Недавно опубликованные работы отмечают положительное влияние изменения образа жизни на частоту развития ФП. Поэтому считается, что раннее выявление ФР и своевременное влияние на них может предотвратить или отсрочить появление ФП. Новые данные говорят о необходимости пересмотра ведения пациентов с ФП и занесения в рекомендации инструкций по изменению образа жизни и модификации ФР. В 2020 г. Американская ассоциация сердца представила научное заявление, в котором освещено взаимосвязь между модифицированными ФР и ФП, оговорено имплементацию стратегий для эффективной модификации ФР, а также выделены направления для новых исследований. Данные, которые есть на сегодня, позволяют сделать вывод, что коррекция ФР способствует снижению частоты возникновения ФП иногда эффективнее абляции и инвазивных подходов. Кроме того, даже когда пациентам показано проведение вышеуказанных вмешательств, модификация ФР ассоциируется с увеличением эффективности этих методик. Однако для

разработки четкой стратегии по модификации ФР необходимо проведение большого числа рандомизированных исследований. Так, целесообразно изучение роли накопления пери / эпикардиального жира в риске и прогрессировании ФП; наиболее эффективных техник, направленных на снижение веса с долгосрочным успехом, и их влияния на течение ФП; влияние высокointенсивных интервальных тренировок на структурное и электрическое ремоделирование левого предсердия; а также уровня гликемического контроля для пациентов с ФП.

Atrial fibrillation (AF) is one of the most common arrhythmias diagnosed in clinical practice. According to forecasts, by 2060 AF will cover more than 18 million people in Europe [8]. Today, AF is a health threat that is constantly growing and is associated with an increased risk of mortality, acute brain disorders and heart failure. This is associated with global population aging, which reflects an important demographic trend today, as well as the prevalence of risk factors (RF).

It is proved that the incidence of AF is directly related to such RF as old age, obesity, hypertension, diabetes, obstructive sleep apnea syndrome, alcohol, tobacco and others [13, 19, 31]. The results of recent studies have indicated a positive effect of lifestyle changes on the incidence of AF [26]. Therefore, it is believed that early detection of RF and timely impact on them can prevent or delay the occurrence of AF. New data suggest the need to review the management of patients with AF and include instructions on lifestyle changes and modifications of RF in the recommendations. Thus, in 2020, the American Heart Association presented a scientific statement, which highlighted the relationship between modified RF and AF, discussed the implementation of strategies for effective modification of RF, as well as identified areas for new research [18].

That is why the purpose of our literary review was to analyze and highlight the latest scientific sources on the modification of RF of AF.

Obesity and atrial fibrillation

The notion of pathogenetic mechanisms responsible for the development of AF has undergone significant changes. The results of scientific research in recent years [6, 21, 25] have shown the impact of obesity on the risk of AF. Thus, the Framingham study of the heart found that obesity is an important predictor of AF in adults. According to scientists, this is caused primarily by the enlargement of the left atrium and the activation of the inflammatory process [25].

Concept of adipose tissue and its function has also changed. Recent studies define that it is not only an energy depot, but also an endocrine and paracrine organ capable of affecting other systems

[2]. The properties of adipose tissue differ depending on the morphology of adipocytes and their localization. Thus, with visceral fat, processes of adipose tissue remodeling develop, which is characterized by the production of more proinflammatory atherogenic cytokines. That is why scientists consider obesity in the context of chronic systemic inflammatory process, which plays an important role in the development of AF.

In addition, an important condition for the development of AF is the presence of structural changes in the heart. Analysis of the scientific literature allows us to conclude about the interaction of obesity and myocardial hypertrophy, dilatation of the cavities of the heart chambers. It has been proven that the accumulation of serum triglycerides in the myocardium leads to myocardial steatosis and increased left ventricular myocardial mass [24].

The results of ARREST-AF and LEGACY studies convincingly demonstrated the presence of a direct correlation between an increase in body mass index and an increased risk of developing AF [6, 21]. In addition, the LEGACY study found the effect of obesity on the frequency of AF recurrences, their duration and clinical picture.

A recently completed REVERSE-AF study examining the effects of obesity and weight loss on AF progression showed that weight loss of $\geq 10\%$ with control of other RF significantly increased the incidence of sinus rhythm recovery [26]. Similar findings were obtained in a prospective open-label study RACE 3, in which a comprehensive correction program of RF was able to control AF more successfully than with a standard treatment [29].

Along with these data, a secondary analysis of a randomized study of Look AHEAD showed that weight loss and exercise did not affect the risk of AF [10]. Interesting conclusions were also made in a large study that included data of more than 55,000 people [17]. After the statistical analysis, the scientists came to the conclusion that of all the anthropometric parameters, it is not the waist, hips and the calculation of their ratio, namely the assessment of body muscle mass that is a significant RF for the development of AF. These data have been confirmed in other studies. Thus, a recent meta-analysis found that big individuals have an increased risk of AF,

and this risk is associated with both weight and height [12]. Thus, people who are obese have an increased risk of developing AF. However, obesity, which is usually determined by BMI, is far from the optimal risk criterion. In addition, according to this meta-analysis, there is growing evidence that the risk of AF is closely associated with increased muscle mass (lean), while there is little evidence of an independent effect of adipose tissue mass. However, weight loss is still appropriate to reduce the risk of AF, but further research is needed to help identify optimal measures to reduce it.

We believe that the discrepancies in the results of a number of studies dictate the need for a more detailed study of this issue.

Physical activity and atrial fibrillation

It is known that hypodynamia is an independent RF of AF development. In 2018, in order to benefit health, the Physical Activity Guideline Advisory Committee recommended to perform 150 minutes/week of moderate-intensity exercises or 75 minutes/week of intense aerobic exercises. Studies have shown that regular aerobic exercises can reduce the risk of developing new cases of AF. The results of the CARDIO-FIT study showed that an increase in cardiorespiratory fitness is associated with a dose-dependent decrease in AF symptoms, and also serves as a predictor of AF recurrence in obese patients [14].

On the contrary, high-intensity exercise, the regularity and duration of which exceeds the figures recommended by the Physical Activity Guidelines Advisory Committee, may increase the risk of developing AF. Thus, a meta-analysis of 6 studies showed that athletes have a 5-fold increased risk of developing AF compared with the control group [4]. Similar conclusions were made in a study that included data of more than 50,000 skiers. It was found that the risk of arrhythmias increases in athletes who reached the finish line earlier and who completed more races [27].

Recently, the population is interested in high-intensity interval training. Compared with continuous moderate-intensity training, the potential benefits of high-intensity interval training include more significant improvements in physiological parameters such as left ventricular ejection fraction, diastolic function, and others. In this context, the study aroused interest, the results of which showed that the performance of high-intensity interval training is associated with a decrease in the time the

patient is in a state of AF (AF burden) for a short period [5].

We should not forget about the so-called mind-body exercises that are in yoga and thai chi. Given the role of the autonomic nervous system in the genesis of AF and the beneficial effects of mind-body exercise on heart function, yoga and thai chi can improve AF management. For example, in YOGA My Heart Study it was found that 3-month yoga classes reduce the time a patient is in a state of AF, as well as improve the quality of life [11].

Syndrome of obstructive sleep apnea and atrial fibrillation

It is known that AF can be caused by non-cardiac causes, among which a significant role is played by obstructive sleep apnea syndrome (OSAS). Studies show a high prevalence of OSAS among patients with AF, which ranges from 21% to 87% [7, 30]. Of the 4395 participants in the MESA study, 181 were diagnosed with OSAS and 1086 with possible OSAS. During the observation period (8.5 years), 212 patients developed AF. The majority of AF cases were observed in the group of people diagnosed with OSAS [20]. The results of the ORBIT-AF registry also showed that 18.2% of AF patients had OSAS. In addition, patients with AF and OSAS have a more severe AF than patients with AF without OSAS. In addition, the frequency of hospitalizations is much higher among patients with AF and OSAS, but the risk of death does not differ in groups [16].

It is worth noting not only the impact of OSAS on the development and progression of AF, but also the effects of CPAP-therapy on the course of AF. A recent meta-analysis demonstrated that CPAP-therapy significantly reduces the risk of AF recurrences and improves cardiac risk control [23].

The relationship between OSAS and AF has been confirmed by a large number of studies. However, it is noteworthy that most of them were observational, so there is a high probability of systematic error. The results of the SAVE study, published in August 2016, also cause some concern [9]. The researchers concluded that CPAP-therapy in combination with standard treatment of cardiovascular pathology, compared only with standard therapy, does not prevent the development of cardiovascular events (including cases of newly detected AF) in patients with OSAS and proven cardiovascular disease.

Therefore, further randomized studies are needed to analyze the relationship between OSAS

and AF, as well as the impact of CPAP-therapy on the course of AF.

Diabetes mellitus and atrial fibrillation

Diabetes mellitus (DM) is considered as a potential RF of AF development. Many studies have reported an increase in the incidence of AF among patients with diabetes. Thus, the results of a large meta-analysis showed that patients with diabetes have a 39% higher risk of developing AF compared with those without diabetes [22]. In addition, there is a direct relationship between the duration of diabetes and an increased risk of AF.

However, not all scientific papers indicate the preservation of a significant correlation between diabetes mellitus and AF after making a statistical correction [32]. The mechanism of AF development on the background of diabetes is not completely clear. The influence of diabetes on the structure and function of the atria is discussed. The results of the Strong Heart Study showed that in patients with AF echocardiographic examination showed a greater mass of the left ventricular myocardium and its wall thickness compared to those without diabetes [15]. Such chronic changes contribute to atrial remodeling and dilatation. In addition to structural changes in the atria, diabetes can lead to electrical, electro-mechanical and autonomous remodeling.

In addition, there is evidence of a relationship between diabetes management and the risk of AF. Some studies have found that aggressive glycemic control is associated with a reduced risk of developing AF [28]. It has been found that glycemic control can also reduce the risk of re-ablation. Thus, blood sugar control is an important strategy in the management of patients with diabetes and AF. However, to date there are no data on the level of glycemic control for patients with AF. Therefore, further research is needed to study this issue.

Arterial hypertension and atrial fibrillation

Epidemiological and clinical studies suggest a close association between the risk of AF and arterial hypertension (AH). Predictable mechanisms of arrhythmia development on the background of hypertension include activation of the renin-angiotensin-aldosterone system, dilatation of the atria, fibrosis and remodeling of the left ventricle with the development of diastolic dysfunction and myocardial hypertrophy [1].

Because inadequate blood pressure control is associated with an increased risk of AF, clinical trials have proven a "lower, better" strategy for the management of patients with hypertension and AF [3]. In addition, taking into account the commonality of RF for hypertension and AF, blood pressure management for AF patients should include not only pharmacotherapy but also modification of RF.

Other risk factors and atrial fibrillation

According to literature data smoking, alcohol, hyperlipidemia, caffeine, ischemic heart disease and cardiac insufficiency may also be RF for AF development (Table).

Implementattion of strategy of lifestyle change

Because AF is associated with many RF, physicians need to focus the patient's attention on lifestyle changes. Treatment of such patients should have a structured and interdisciplinary approach. Based on research data for patients with AF in order to reduce the risk of arrhythmia it is considered appropriate [18]:

1. In the presence of obesity to reduce body weight by 10%, $BMI < 27 \text{ kg/m}^2$, increase physical activity by 2-MET. Use bariatric surgery if necessary.
2. Encourage regular physical activity of moderate intensity. In order to improve the patient's commitment to regular exercise, high-intensity interval training is recommended.
3. Carry out screening and treatment of concomitant OSAS.
4. Monitor blood sugar levels. If necessary, it is recommended to take drugs and change lifestyle in accordance with current recommendations.
5. Monitor blood pressure figures. If necessary, it is recommended to take drugs and change lifestyle in accordance with current recommendations.
6. In the presence of concomitant heart failure to optimize drug therapy (including AMR) and change lifestyle in accordance with current recommendations.
7. Consult to reduce the dose of alcohol and quit smoking.

Other risk factors and atrial fibrillation [18]

Risk factors	Relationship with AF	Impact on AF	Comments
Ischemic heart disease	IHD and AF have similar RF. Ischemia of atria as a rule is accompanied with their remodeling.	There are data on antiarrhythmic effect of β -blockers in IHD patients.	β -blockers may be used both in treatment of IHD and AF. Management of patients should include RF modification.
Cardiac insufficiency	Patients with HF have an increased risk of developing AF. Cardiomyopathy leads to atrial remodeling, and, as a consequence, to the development of AF.	Retrospective analysis showed a decrease in the frequency of AF with the use of β -blockers, ACEI inhibitors, ARB, AMR. RACE 3 shows that AF correction can control AF more successfully than standard treatment alone. The advantages of catheter ablation over antiarrhythmic therapy in patients with AF and HF have been demonstrated.	Treatment of patients with AF and HF should include modification of RF as well.
Lipids	Data on the relationship between hyperlipidemia and AF are very contradictory. The data available today do not allow the use of PUFA or statins for the prevention of AF.	Statins have anti-inflammatory and antioxidant effects. Statins have a potential protective effect on atrial remodeling. PUFA did not show a significant reduction in AF recurrence.	The data available today do not allow the use of PUFA or statins for the prevention of AF.
Tobacco smoking	Tobacco smoking is associated with an increased risk of AF. The relationship between smoking and the risk of AF is dose-dependent. COPD is an independent RF of AF development. Smoking negatively affects the effectiveness of ablation.	Data on the decrease of incidence of AF development when smoking is ceased are absent.	As a prevention of AF, it is recommended to support and advise the patient to cease smoking.
Alcohol	Alcohol leads to atrial remodeling, and as a consequence – AF development.	Abstinence from alcohol is associated with improved rhythm control.	AF patients who regularly take medium and high doses of alcohol should be advised to reduce alcohol intake.
Caffeine	Data on the relationship between caffeine and AF are contradictory. There are reports of a possible protective effect of low and high doses of caffeine.	There are no data on the positive effect of reduced doses of caffeine on the development of AF.	There is no evidence that caffeine is a significant RF in the development of AF. Some studies suggest a possible protective effect of caffeine.

Notes: AMR – antagonists of mineral-corticoid receptors; ARB – angiotensin receptor blocker; ACEI – angiotensin converting enzyme inhibitors; IHD – ішемічна хвороба серця; PUFA – polyunsaturated fatty acids; HF – heart failure; AF – arterial fibrillation; RF – risk factor; COPD – chronic obstructive pulmonary disease.

CONCLUSIONS

To date, the focus of AF treatment is on the use of valuable techniques and drugs, while the modification of most RF does not require the use of invasive and pharmacological agents. At the same time, optimal RF control is associated with the preservation of sinus rhythm in 40% of patients without the need to use rhythm control strategies. The data available today allow us to conclude that the correction of RF contributes to the reduction of the

frequency of AF and is sometimes more effective than ablation and invasive approaches. In addition, even when patients are shown to perform the above interventions, modification of RF is associated with increased effectiveness of these techniques. However, to develop a clear strategy for the modification of RF requires more randomized trials.

Conflict of interest. The authors declare no conflict of interest.

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