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Risk assessment for atrial fibrillation in metabolic syndrome depending on the primary prevention strategy

Olesin A.I., Konstantinova I.V.

North-Western State Medical University named after I.I. Mechnikov, St. Petersburg, Russia

Authors

Alexander I. Olesin*, M.D, PhD, Professor of Medicine, North-Western State Medical University named after I.I. Mechnikov, St. Petersburg, Russia.

Irina V. Konstantinova, M.D, PhD, Associate Professor of Medicine, Department of Internal Medicine, North-Western State Medical University named after I.I. Mechnikov, St. Petersburg, Russia.

Today, obesity in the form of metabolic syndrome (MS) and atrial fibrillation (AF) have reached epidemic proportions according to World Health Organization (WHO). AF is present in over 34 million people worldwide and this number is expected to double by 2060. In 25% of patients MS is associated with the development of AF. Although new treatment approaches have emerged over the last years, AF is still associated with an increased risk of complications such as systemic thromboembolism, congestive heart failure (CHF), stroke, myocardial infarction (MI) and other. Thus, AF poses both social and economic problem for healthcare in the most countries due to significant treatment expenses.

In the following review article we analyze the existing approaches to prevent AF in patients with MS depending on the initial risk of its development.

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* Corresponding author. Tel. +79213295292.E-mail: olesin58@mail.ru

Introduction

Over the last years, the prevalence of obesity has reached the pandemic proportions: approximately 2 billion people are overweight, 650 million have abdominal obesity (AO) mostly associated with metabolic syndrome (MS) [1, 2]. In Russia, MS is present in 30 % of population [2]. MS is a leading cause of atrial fibrillation (AF) and includes the number of risk factors such as AO, arterial hypertension (AH), hyperglycemia and hyperlipidemia [2]. AF is the most common arrythmia in the clinical practice and is associated with the increased risk of mortality, stroke, and other complication [3]. Once it has developed, AF relapses in the majority of cases and eventually progresses from paroxysmal to persistent and then to permanent form [4]. There are many well-known AF risk factors such as obesity, AH, diabetes, heart defects, various clinical types of coronary artery disease (CAD), hyperthyroidism, alcohol use, OSA, electrolyte and/or vegetative dysregulation and other [4]. A surge of MS and AF prevalence has been registered in many countries and the number of AF cases is expected to rise from 8.8 million in 2010 to 17.9 million in 2060 [5]. Currently, MS causes around 35 % of AF cases [1, 2].

Therefore, identification of patients with MS at high risk of AF and the development of prevention approaches is one of the most relevant challenges of clinical cardiology today.

Metabolic syndrome, its components and atrial fibrillation

The main cause of MS is primary, genetically determined insulin resistance and hyperinsulinemia. The term "metabolic alteration" was first introduced by K. Jahnke et al (1969) and "metabolic syndrome" — by M. Hanefeld and W. Leoonardt (1981) when they combined various metabolic alterations in overweight patients [2]. In 1988 G. Reaven described insulin resistance as the cause of MS [2].

Currently the diagnosis of MS is based on the following main and additional criteria (metabolic syndrome is present if three or more of the following five criteria are met) [2]:

Main criterion: waist circumference over 94 cm (men) or 80 cm (women);

Additional criteria:

Blood pressure values of systolic 130 mmHg or higher and/or diastolic 85 mmHg or higher or normal blood pressure values achieved with antihypertensive drugs.

Elevated triglycerides>1.7 mmol/l; reduced high-density lipoprotein cholesterol (HDL)<1.0 mmol/l in men and<1.2 mmol/l in women; elevated low-density lipoprotein (LDL)> 3.0 mmol/l;

Elevated fasting glucose> 6.1 mmol/l.

Impaired glucose tolerance — plasma glucose 2 hours after glucose tolerance test>7.8 and< 11.1 mmol/l.

Pathophysiologic processes that lie behind the development of AF in MS patients is complicated and multifactorial. In most cases the increased body mass index (BMI) is associated with higher risk of arrythmia development [2, 3, 6]. A few studies have shown that the rise of BMI by 1 kg/m^2 from the baseline of more than 30 kg/m^2 is associated with 4 % rise of AF risk per year regardless of gender and presence of diabetes or AH [6, 7].

Individuals with MS were observed to have the "obesity paradox" that refers to lower mortality and lower prevalence of AF in patients with higher MBI [8]. Longitudinal prospective studies have shown lower lethality in overweight patients (BMI 25–29 kg/m^2) and in patients with AO (BMI 30–35 kg/m^2) with AF and other cardiovascular disease [7, 8, 9].

AO and high BMI in MS is associated with higher circulating blood volume, cardiac output and ejection fraction that leads to left ventricular (LV) hypertrophy and left atrial (LA) diastolic dysfunction and dilation [2, 3, 4]. Progressive LV hypertrophy and dysfunction can provide a substrate for the development of atrial fibrillation [4, 5, 10].

In patients with MS the risk of AF correlates with the growth of epicardial adipose tissue (EAT) including the LA EAT [11, 12]. The important physiologic functions of epi- and pericardial adipose tissue include thermoregulation, energy accumulation and mechanical protection as well as the parasympathetic regulation of cardiac function. [10–12]. Moreover, EAT produces many pro- and anti-inflammatory adipocytokins, growth factors and metabolic substrates and diffuse directly into the cardiac muscle [10–12]. In patients with MS and AF EAT contained more CD45+ (lymphocyte common antigen), CD3+ T-cells, CD68+ cells (dendritic cells marker), tumor necrosis factor α (TNF-α), IL-1β, IL-6, right atrial nuclear factor kappa B (NF-κB) compared with patients without arrythmias. Moreover, higher TNF-α and L-6 concentrations strongly correlated with fibrosis and atrial lymphomonocytic infiltration [13, 14]. Therefore, local EAT inflammation induced by immune cells and regulated by cytokines is one of the mechanisms of AF development in MS [13, 14].

Apart from inflammation, another important substrate for AF development is myocardial fibrosis in both atria (primarily in the posterior wall of LA) [3, 4, 6, 8] caused by inflammatory cytokines and growth factors such as activin A and matrix metalloproteinase [15, 16]. Activin A belongs to the TGF-β family and induces the expression of TGF-β1 and TGF-β2 [15, 16]. Experiments have shown that TGF-β1 caused atrial fibrosis and increased the risk of AF due to the re-entry waves [15–17].

Apart from AO, other MS components such as AH, diabetes, hyperlipidemia can increase the risk of AF due to fibrosis and structural remodeling of atrial myocardium that lead to the development of various electrophysiologic effects and AF [17].

AH is associated with increased activity of renin-angiotensin-aldosterone system, active aldosterone synthesis by adipocytes and the increase of BMI lead to the progressive LV dysfunction and LA dilation [15–17]. Hyperglycemia and hyperlipidemia in MS are associated with atrial hypertrophy and fibrosis that develop because of the effects of glycation products, TGF-ß, inflammatory cytokines and other metabolic substrates [15–17].

Of note is that the use of alcohol, coffee, smoking, OSA and atrial premature complexes (APCs) can cause LA fibrosis and increase the risk of AF in patients with MS [3, 4, 8].

Currently obstructive sleep apnoea (OSA) is one of the new predictors of AF in MS [18, 19]. Various clinical studies have shown that patients with MS and OSA are at a 4 times higher risk of AF development compared with the patients without respiratory problems during sleep [18, 19]. Similar results were shown in patients with MS who abuse alcohol, coffee, energy drinks, smoking compared with patients without these bad habits [17].

AF in MS due to OSA, overuse of coffee, alcohol, energy drinks and smoking is caused by several mechanisms. Firstly, hypoxia and hypercapnia at the end of apnoea episode leads to activation of the sympathoadrenal system and blood pressure elevation [18, 19]. Secondly, intensive inhaling at the end of apnoea episode increased intrathoracic pressure that led to LA overdistention [18, 19]. Thirdly, hypoxia, hypercapnia, and excessive parasympathetic stimulation due to the vagal activation shortened the effective refractory period and increased the dispersion of impulse conduction in the atria and AF development [18, 19]. Moreover, during the OSA episode pressure in the trachea became negative and that slowed the recovery of cardiac muscle refractoriness and increased AF induction [18, 19]. Lastly, alcohol, caffeine, nicotine, and energy drinks increased the activity of systemic inflammatory "oxidative stress" mediators in patients with MS that, apparently, caused the formation of fibrotic areas and AF [17–19].

However, the effects of OSA alone and in combination with other factors still require further exploration. Therefore, the degree of OSA effects on the development of arrythmia in MS still need to be determined.

Currently the mechanisms of AF development in MS still require further investigation [2, 3]. Lately the theory of AF development due to the diastolic calcium ions overload is being studied [16, 17]. Calcium ions overload initially results into oxidative stress and the appearance of areas with uneven impulse conduction and refractoriness and then — the activation of trigger mechanisms and/or re-entry and development of atrial ectopy [3, 16, 17]. APCs then act as drivers. They form rotors in the posterior LA wall and cause the formation of paroxysmal or persistent or permanent AF [3, 4]. Patients with MS and AF only rarely have the ectopic areas in atria and/or ectopic activity in pulmonary veins [3, 4].

Atrial fibrillation risk assessment in patients with metabolic syndrome

Currently, pulse palpation is recommended for timely diagnosis of AF in all patients, especially in those over 64 years of age. In patients with arrhythmic pulse ECG is performed [3]. However, this approach results in many false positives and increases the load on primary healthcare [20]. The use of automatic or semiautomatic tonometers with ECG registration can significantly reduce the number of false positives and improve AF diagnosis [20]. Lately, a high-risk group of AF development was established among patients over 65 with MS according to the CHA2DS2VASc thromboembolic events risk scale≥1 — in men and≥ 2 in women: these patients are recommended to perform everyday pulse measurements and check the rythm [20–22]. The frequency of AF diagnosis in patients with CHA2DS2VASc score 1–2, 5–6 and 9 was 10 %, 54 % и 71 %, respectively [21, 22].

In the recent years over 21 risk-stratification scales have been proposed for AF risk assessment in MS patients, including Framingham scales (1944–2014) [23]. Meta-analysis has shown that CHARGE-AF scale was most useful for predicting 5-year risk of the first AF episodes [24]. CHARGE-AF includes simple and

common values such as age, gender, anthropometric measures, blood pressure, etc. [23]. For AF risk assessment CHARGE-AF uses the following formula:

$$\text{RiskCHARGE-AF} = 1 - 0.9718412736^{\exp[(\Sigma(B_1,B_2,B_3,B_4,B_5,B_6,B_7,B_8,B_9,B_{10},B_{11}) - 12.5815600]},$$

Where RiskCHARGE-AF — AF risk according to CHARGE-AF (in units), B1-(age in years/5) ×0.5083; B2-ethnicity (Caucasian: 1x0.46491); B3 — (height in cm/10)×0.2478; B4 — (weight in kg/15) ×0.1155; B5 — (systolic blood pressure in mmHg.÷10)×0.1013, B7 — current smoking (1×0.35931), B8 — antihypertensive therapy(1×0.34889), B9 — diabetes(1×0.23666), B10 — history of myocardial infarction (1×0.49659). If the risk of AF was close to 1.0 according to CHARGE-AF, for example, 0.8 and more signified a high 5-year risk of AF. Of note is that in almost all patients with MS, especially in those over 60 years old, the risk of AF development was high according to CHARGE-AF [24]. Accuracy of 5-year prognosis was around 50 % [25].

In other studies, the risk of AF development was assessed using dynamic follow-up models [26, 27]. Based on the 10-year follow-up 1968 MS patients without arrythmias [26] and 1427 — with APCs but without AF prior to the study, were included [27]. According to the results, identification of AF predictors such as LA dilation, LVEF reduction, transmitral flow spectrum reduction, APCs etc after one examination of patients with BMI>30 kg/m^2 determined the presence of this potential risk factor but couldn't provide any time frame of AF development [26]. In turn, a specific time frame when AF can potentially develop, for example, in a patient with MS and APCs can be determined only with follow-up based on the risk index of AF [26, 27]. AF risk index can be calculated using the following formula: [(A÷B) × (C÷D)], where A — filtered P-wave duration in the atrial ECG (m/s), B-Pd (m/s), C — A — linear deviation of corrected preectopic interval (ms) for at least 20 atrial extrasystoles, D-number of atrial extrasystoles per hour [26, 27]. AF risk index is calculated several times with 1–3-month intervals. The development of AF is likely if the index values decrease compared to baseline [26, 27]. Specific time frame of AF development depends both on the baseline AF risk index values and the time during which it decreased to minimal levels when AF developed (0.01–0.02 units) [26, 27]. If the speed of AF risk index reduction is known, a specific time frame in which AF will develop in patients with MS can be easily calculated [26, 27]. The accuracy of certain time-period determination using the follow-up model is around 90 % [26, 27].

Therefore, the assessment of 5- or 10-year AF risk was based mostly on the retrospective analysis of various risk-stratifying models or prospective studies on relatively small samples of patients with MS [23, 26, 27]. Thus, apparently, larger multicenter prospective studies are required to increase the accuracy of predicting the first AF episodes and determine more specific time periods for these episodes (from several months to 1 year).

The choice of atrial fibrillation prevention strategy in patients with metabolic syndrome

All components of metabolic syndrome (AO, AH, hyperlipidemia, impaired glucose tolerance or diabetes) as well as overuse of alcohol, coffee, energy drinks, tobacco smoking, lack of physical activity, OSA and APCs can be classified as potentially modifiable AF risk factors.

Currently three strategies of AF prevention are being discussed [28, 29].

1) Modification of certain MS components are negative risk factors.

2) Complex lifestyle modification with all risk factor correction.

3) The use of antiarrhythmic agents to suppress APCs in patients with MS at a very high risk of AF development in several months to 1 year [28, 29].

Abdominal obesity. Reduction of waist circumference to normal measurements (<80 cm in women and<94 cm in men) and BMI to<25 kg/m^2 decreases the risk of AF by 18–20 % [28, 29]. In most cases, special diets and/or aerobic physical activity are used to reduce BMI. The most effective method of reducing BMI and waist circumference in MS patients was the use of Mediterranean diet [28, 29]. BMI reduction by>10 % in patients with MS was associated with better myocardial contractility, improved LV dysfunction and decreased LA volume and EAT mass [28, 29]. If BMI reduction attempt was unsuccessful in case of baseline BMI>30 kg/m^2 and the presence of all MS components in a patient adherent to regular physical activity, healthy diet etc surgery is the best approach [28, 29].

Controlling plasma glucose levels in patients with metabolic syndrome and diabetes. In patients with MS and diabetes controlling plasma glucose and Hba1c levels and was associated with AF risk reduction by 2.5–3 % [28, 29]. Hypoglycemic therapy of choice in

patients with MS and diabetes includes metformin, glucose-like peptide 1 agonists (liraglutide) or sodium-glucose linked transporter 2 inhibitors (empagliflozin) that normalize plasma glucose levels, help reduce BMI, EAT mass and inflammatory cytokine activity [28, 29]. Previous evidence has shown that the addition of these agents leads to additional AF risk reduction by 5 % or more [28, 29].

Blood pressure control. Reaching target blood pressure values<130/85 mmHg reduces the risk of AF by 20 % [28, 29]. The most effective antihypertensive agents were angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), diuretics and beta-blockers [28, 29]. Positive effects of blood pressure control are reversion of heart structural remodeling and improvement of LV dysfunction, LA volume and LV myocardium mass [28, 29].

Blood lipid control. Blood lipid control with statin use was associated with 5 % AF risk reduction in patients with metabolic syndrome; total cholesterol<3.5 mmol/l additionally reduced arrythmia risk by 5 % [28, 29].

Aerobic physical activity. Moderate or high intensity everyday physical activity for 60–90 minutes [28, 29] reduces BMI, waist circumference, LV dysfunction, LA volume and AF risk in patients with metabolic syndrome (additionally to weight loss) by 9–12 % (depending on the baseline BMI and physical activity intensity and duration) [28, 29]. Of note is that in patients with metabolic syndrome at high risk of AF (year after the exam) who used kinesiotherapy (walking speed modulation depending on the heart rate twice a day and more) for at least two hours a day reduced the risk of AF by 70 % compared with the use of first-line therapy (blood pressure, glucose, and lipid control) [28, 29].

Smoking in metabolic syndrome. Smoking cessation reduces the risk of AF by 10 % [28, 29].

Alcohol, coffee, energy drinks use in metabolic syndrome. Avoidance of alcohol, coffee and energy drinks wasn't associated with decreased AF risk in MS patients [28, 29]. The amount of alcohol that doesn't affect the risk of AF in metabolic syndrome is 10 grams of 96 % ethanol per day (equivalent to 60 ml of 40° alcoholic beverages, 240 ml of 9–12° red wine and 660 ml of beer) [28, 29]. Consumption of up to 436 mg of caffeine in coffee or tea per day or up to 660 ml of energy drinks per day didn't increase the risk of AF in metabolic syndrome [28, 29] (one cup of espresso from a coffee machine contains 65–75 mg of caffeine, latte — 30–35 mg, cappuccino — 30–35 mg, americano 80–85 mg, one tea bag — 30 mg for black tea and 25 mg for green teat) [28, 29].

Antioxidants, polyunsaturated fatty acids. Addition of various antioxidants, omega 3-6-9 polyunsaturated fatty acids didn't reduce the risk of AF in patients with metabolic syndrome [28, 29].

Obstructive sleep apnoea management in patients with metabolic syndrome. To alleviate the negative effects of OSA negative pressure continuous positive airway pressure (CPAP) is used. A CPAP machine uses a tube and a face mask to deliver constant and steady air pressure [28, 29]. However, preliminary evidence has shown that AF risk reduction is no more than 5 % [28, 29].

Managing atrial premature contractions in metabolic syndrome. In most cases APCs are considered to have favorable prognosis and don't require pharmacologic therapy except for symptomatic extrasystoles [3]. On the other hand, frequent, stable and/or relapsing APCs can increase the risk of AF because they create uneven electrical impulse conduction in atrial myocardium [26, 27]. Antiarrhythmic agents used in APCs in patients with metabolic syndrome are usually used in individuals at high and very high risk of AF, for example, in the next several months to a year [28, 29]. The studies that investigated the use of antiarrhythmics in APCs in MS for prevention of AF are limited, probably due to high risk of adverse effects of this therapy [29]. Control of APCs in MS reduced the risk of AF by 68 % compared with the use of therapies that control blood pressure, blood glucose and lipid levels [28, 29]. In the absence of pharmacologic therapy effects ablation can be performed [28, 29].

Anticoagulation for thromboembolism prevention in patients with metabolic syndrome at high risk of AF. The International Society on Thrombosis and Haemostasis (ISTH) recommend the use of anticoagulation in patients with metabolic syndrome for deep vein thrombosis, thromboembolic events, and stroke prevention. In patients with BMI⩽40 kg/m^2 or weight⩽120 kg direct oral anticoagulants are recommended (dabigatran, rivaroxaban, apixaban, warfarin); in those with higher values of BMI and weight — only warfarin [30]. AF risk determined by CHARGE-AF highly correlated with potential thromboembolism according to CHA(2)DS(2)-VASc [23]. Therefore, theoretically, 2 and more points according to CHA(2)DS(2)- VASc in patients with metabolic syndrome at high risk of AF can require anticoagulation (bleeding risk according to HAS-BLED [3] should be taken into consideration). Currently there are ongoing studies that investigate the use of anti-

coagulants in patients with MS depending on both the AF risk and thromboembolism risk, stroke. Rhythm abnormalities will be determined with continuous ECG monitoring with loop recorders [3].

Complex lifestyle modification in patients with metabolic syndrome. Complex approach to potentially modifiable AF risk factors and MS components can reduce the risk of AF by 50 % according to the results of retrospective studies [28, 29]. However, to assess the real AF risk reduction in patients with metabolic syndrome large prospective randomized studies are needed.

Conclusion

Over the last years the prevalence of atrial fibrillation has been rising steadily. Considering that AF is associated with a high risk of thromboembolic events and heart failure progression, primary prevention measures need to be developed.

Controlling the modifiable risk factors such as AO, AH, diabetes, impaired glucose tolerance, hyperlipidemia, OSA and others can reduce the risk of atrial fibrillation by 20 % if these risk factors are managed separately and by over 50 % is they are managed together. Therefore, following a healthy lifestyle starting from a young age, including healthy diet, physical activity, low alcohol intake and avoidance of smoking will be the mainstay of AF primary prevention in patients with metabolic syndrome.

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