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PREVENTION OF ATRIAL FIBRILLATION BEYOND ANTIARRHYTHMIC DRUG THERAPY – MULTIFACTORIAL APPROACH

PREVENÇÃO DA FIBRILAÇÃO ATRIAL ALÉM DO ANTIARRÍTMICO – ABORDAGEM MULTIFATORIAL

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ABSTRACT

AF (atrial fibrillation) prevention involves an individualized, multidisciplinary, and integrated approach taken by the patient, which which goes beyond the arrhythmia per se. Because it is a multifactorial arrhythmia with complex pathophysiology, patients with AF should undergo a complete assessment, including electrocardiographic and electrophysiological studies, lifestyle modifications, and optimization of chronic diseases, such as hypertension and heart failure. In this article we describe the main interventions studied in the literature that are beneficial in the prevention of atrial fibrillation.

Keywords: Atrial Fibrillation; Secondary Prevention; Arrhythmias, Cardiac.

RESUMO

A prevenção da fibrilação atrial (FA) envolve uma abordagem individualizada, multidisciplinar e integrada do paciente, que vai além da arritmia per se. Por se tratar de uma arritmia multifatorial e com fisiopatologia complexa, os pacientes com FA devem ser avaliados em sua integralidade, que inclui aspectos eletrocardiográficos, eletrofisiológicos, medidas comportamentais e otimização de tratamento de doenças crônicas, como hipertensão arterial e insuficiência cardíaca. Neste artigo descreveremos as principais intervenções estudadas na literatura com benefício na prevenção da fibrilação atrial.

Descritores: *Fibrilação Atrial; Prevenção Secundária; Arritmias Cardíacas.*

INTRODUCTION

The most common sustained arrhythmia found in clinical practice is atrial fibrillation (AF), with an overall incidence of 0.5-1.0%. AF is associated with age and gender; it is uncommon in women under 40 years old and common in men over 80 years old.[1-5] AF causes significant reduction in quality of life by promoting exposure to anticoagulation and its risks, increasing rates of stroke, palpitations, and syncope, and increasing risk of sudden death, as in the case of patients with pre-excitation syndrome. In addition to the clinical impact, AF increases healthcare expenditures, especially due to hospitalizations.[3,6] Based on data from the Framingham cohort,[7] it is estimated that after the age of 40 years, one in four people develops AF.[7, 8]

With rates of epidemic proportions, about five million patients are estimated to have AF in the United States by the year 2050, and its incidence is expected to triple every 10 years.[1-3,9] Therefore, we emphasize that measures to prevent or delay the onset of AF can reduce healthcare expenditures and improve the quality of life of these patients.[6,10]

AF is the is the arrhythmia with with the highest number of associated comorbidities and risk factors.[11] Causal factors can be divided into cardiac (structural, arrhythmic, and genetic), non-cardiac (pathological: diabetes mellitus, hyperthyroidism, chronic obstructive pulmonary disease, etc.; or physiological: endurance training and advancing age), and those related to surgical interventions, substance use or abuse.[11,12] The fact that AF is the final manifestation of so many pathways is one of the factors making its prevention so complicated: obesity, obstructive sleep.

Obesity,[13] obstructive sleep apnea/hypopnea syndrome (OSAHS),[14] heart failure,[15] mitral and/or aortic valve disease,[16] and systemic arterial hypertension (SAH) are just a few modifiable risk factors associated with AF, allowing for the development of clinical interventions that may affect the disease.[12,17]

Regarding the electrophysiological process, atrial fibrillation requires two components: an arrhythmia trigger and a substrate capable of supporting it.[18] Ectopic atrial beats, especially from the muscle sheath of the pulmonary veins, are the most common triggers. The frequent activation of such foci alters the cellular transmembrane electrical currents and shortens the duration of the action potential. The substrate can be the result of a remodeled, dilated left atrium, with fibrosis and chronic inflammation and the formation of circuits

for micro and macroreentries. The mechanisms responsible for sustained fibrillation conduction within the atria are based on the formation of wave fronts that are fragmented into multiple random reentry foci. The shortening of atrial refractivity allows for rapid tissue response when atrial ectopias are rapidly triggered. When this phenomenon occurs beyond the limit, it can destabilize the atria. Otherwise, when it occurs under appropriate conditions, it generates atrial fibrillation. This condition (fibrillation conduction) is generated when an atrial stimulus or wave front occurs in the trail of atrial refractivity of the previous cycle and the tissue has not yet recovered its maximum conduction capacity, which favors the fragmentation of atrial electrical activity and underlies the mechanism of reentry.[18,19]

A comprehensive approach for patients at risk of developing AF is critical for both the prevention or delay of this arrhythmia and for improvements in the clinical outcomes of those already using drugs or undergoing non-pharmacological therapies, such as catheter ablation.[4,12,20]

It is up to the clinician to guide the patient, both to control comorbidities and to promote lifestyle changes to prevent or delay at the onset of AF. Clinical compensation (physical, psychological, and biological) is fundamental for the management of this arrhythmia. The main modifiable factors for the management of patients at risk of developing AF are listed below.

ASSOCIATED MODIFIABLE FACTORS

Cardiac Insufficiency

Considering the functional class established by the New York Heart Association, the prevalence of AF in these patients is between 13 and 27% with an incidence varying from 4 to 41% over time, regardless of the ejection fraction of the left ventricle.[15, 21]

Heart failure and AF often occur together, with an increased risk of one in the presence of the other. They have a similar epidemiological profile and a higher incidence with advancing age.[15]

The main pathophysiological changes involve tissue distension of the atria caused by increased volume and pressure due to congestion, resulting in atrial stretching and reduction of its effective refractory period. Ionic overloads related to myocyte stretching lead to calcium changes, which increase the occurrence of potential postoperative and atrial activity and contribute to the pathophysiology of AF.[22] Moreover, the hormonal activation from the renin--angiotensin-aldosterone system (RAAS) perpetuates mechanisms of fibrosis in the extracellular myocardial matrix, with areas of conduction delayed or blocked favoring the occurrence of microreentries. The angiotensin II enzyme can increase the activity of cardiomyocytes in the sheaths of pulmonary veins.[23]

The use of angiotensin-converting enzyme inhibitors (ACEI) favors the prevention of AF by inhibiting fibrosis and improving the hemodynamic profile.[24-26] However, there is still no formal recommendation for its use in the primary prevention of AF. Other drugs routinely used in the treatment of heart failure were listed as options in the primary prevention—e.g. statins, aldosterone inhibitors—but still have not been adequately investigated.[27,28]

Smoking

The ARIC[1] and Rotterdam[29] studies clearly showed an association between AF and smoking. Active and former smokers when compared to have an increased risk of AF (up to up to 2-fold) compared to the control group of individuals who have never smoked. There seems to be a dose-dependent effect on risk. Other forms of exposure to tobacco did not show the same association.

Similarities, such as such as pumonary injury and stimulant substances, are considered the culprits for the association, are considered responsible for the association between smoking and AF. Especially because these similarities reduce pulmonary function and predispose individuals to acute coronary events.[30] Smoking can be considered a potential marker of deprivation (social, food, and well-being) and of a poor lifestyle.[11,16,30,31]

There is still no evidence that smoking cessation prevents AF, but there is consensus that the reduction of atrial and pulmonary damage reduces the probability of progression to AF.[4]

Systemic Arterial Hypertension

Based on data from the ARIC study, SAH is estimated to be responsible for up to 20% of the risk of developing AF. [1,32] The incidence of AF in hypertensive patients over 55 years of age is 38%, and it increases to 70% in patients 75 years old. It is worth mentioning that the association of SAH with atherosclerotic disease represents an even greater risk and a worse prognosis in the presence of AF.[4]

After causing the increase in sympathetic tonus, with the subsequent increases in left atrial pressure and volume, and perpetuation of SARS-related injuries, atrial remodeling may facilitate the onset of AF. Adequate pressure control can lead to reverse ventricular remodeling and reduce the frequency of AF paroxysms.[33]

In general, the aim is to maintain systolic pressure around 120 to 130 mmHg. Pressures below these values were associated with the incidence of AF.[26]

Clinical studies reported lower incidence of AF in patients who were treated with ACEI or angiotensin II receptor blockers (ARBs) than in those treated with beta-blockers, especially in the presence of left ventricular hypertrophy and ventricular dysfunction.[21,25,26]

Further analysis from a Danish cohort showed that initial treatment of uncomplicated hypertension with ACEI or ARBs reduces the incidence of AF when compared to other antihypertensives. ARB therapy did not reduce the incidence of AF in patients without structural heart disease. The use of ACEI or ARBs may also reduce AF recurrence after electrical cardioversion.[34]

The role of aldosterone antagonists in the management of AF has not yet been investigated. Although studies analyzing eplerenone have shown favorable results in primary prevention, there is still no robust evidence for the use of aldosterone antagonists in secondary prevention of AF. [27,28,35]

Alcohol Consumption and Use of Stimulants

Recent meta-analyses showed an 8% increase in the risk of AF per 10 mg/day of ethanol ingested. [36,37] In addition to being an independent factor for AF, regular consumption

increases the risk by 5% (35% *vs.* 40%) after the age of 55. The consumption of distillates is associated with greater risk of AF.

In Swedish prospective cohort study, Larsson et al. followed 79,000 men and women without AF for up to 12 years (1998-2009) and found 7,245 incidental cases of AF.[38] Data analysis did not show an association between AF and gender, but it showed an association with dose--dependent alcohol consumption, even after the exclusion of the individuals who were alcoholics. (Table 1) Interestingly, they also compared the different types of alcoholic beverages most commonly consumed, such as distillates, wine, and beer. They concluded that, although there was a correlation between alcohol (dose-dependent) and AF, beer consumption alone did not show this association.

From the pathophysiological point of view, the combination of cellular and autonomic deleterious effects of ethanol results in electrophysiological changes capable of promoting atrial reentry and AF. Damage to intercellular junctions and channels, inflammation, direct lesion to atrial myocytes, vagal inhibition, sympathetic activation, and reduction of heart rate variability

Chart 1. Association between ethanol dose and relative risk of AF.

Dose/week (12g ethanol/dose)	Relative risk (Confidence interval)
1-6 doses	1.01 (0.94-1.09)
7-14 doses	1.07 (0.98-1.17)
15-21 doses	1.14 (1.01-1.28)
> 21 doses	1.39 (1.22-1.58)

Adapted from Larsson et al., 2014.

taken together shorten the effective refractory period and trigger this arrhythmia.[36,38-40] The toxic effects of ethanol also slows the pace of intra- and interatrial conduction, facilitates conduction in the atrioventricular node, promotes diuresis by inhibition of the antidiuretic hormone, and reduces the serum levels of some electrolytes (e.g., potassium and magnesium) further facilitating the onset of AF.[37,41-43]

Caffeine consumption, even at high levels (up to 10 cups of coffee or 1.0 g/day) was not a risk factor for AF if consumed alone. The consumption of energy drinks with taurine and caffeine has already been considered an AF trigger, especially when used with distillates.[4,12]

The increasingly frequent use of cannabis has also led to AF in young patients without comorbidities. Excessive use can lead to persistent electrical remodeling and can be harmful in elderly patients with comorbidities.[31] It is believed that adrenergic stimulus associated with decreasing microvascular flow acts as a facilitator in AF.[5,40,44]

Drugs

Drug-induced AF is underdiagnosed and clinically underestimated. Several drugs have been described as AF inducing—notably adenosine,[45] dobutamine,[46] non-steroidal anti-inflammatory drugs, corticosteroids ,and chemotherapy.[40] The main risk factors for drug-induced AF are polypharmacy, hypertension, structural disease, chronic obstructive pulmonary disease (COPD), and OSAHS.[40]

When adenosine is used for the reversal of supraventricular paroxysmal tachycardias with involvement of the atrioventricular node, it may cause AF.[40,45] Dobutamine, especially in cardiac postoperative period, is also a common cause of AF.[40,46]

In chemotherapy treatment, attention should be given to the use of anthracyclines, melphalan, interleukin-2, and cisplatin.[47] The administration of ondansetron was also reported as a potential AF trigger.[40]

Sleep Disorders

One factor that should always be investigated in patients with AF is the possibility of sleep disorders, especially OSAHS. Screening for OSAHS in all patients with AF is recommended according to a recent article published by the Heart Rhythm Society, in which up to 80% of electrophysiologists questioned patients in search of signs and symptoms of sleep disorders before performing catheter ablations.[48] Regardless of the cause, sleep deprivation is an independent risk factor for the development of AF.[4,11,14]

Sleep-related ventilatory disorders include obstructive sleep apnea, central sleep apnea, periodic breathing (e.g. Cheyne-Stokes breathing), and sleep-related hypoventilation. OSAHS affects approximately 24% of men and 9% of women between 30 and 60 years of age.[48] Several studies have reported that the prevalence of OSAHS is substantially higher among patients with AF (32 to 39%), indicating that this disease contributes to the onset and progression of AF. [14,49]

In isolation, OSAHS has a risk ratio for AF recurrence of 2.18.[48] Multiple pathophysiological mechanisms may contribute to AF, including dysautonomia, hypoxia, hypercapnia, and inflammation. The exaggerated increase in intrathoracic pressures by itself and when associated with vagal activation shortens the potential for atrial action and may induce AF.[14]

Control of comorbidities and the use of positive pressure ventilation, the treatment of choice, can reduce AF recurrence. Positive pressure prevents the collapse of the pharyngeal region and relieves airway obstruction. Bilevel or adaptive pressure ventilation can be used in patients that are intolerant to continuous positive airway pressure (CPAP). Other therapeutic modalities include the use of mandibular devices, surgery for upper airway clearance, and lifestyle changes. The treatment of OSAHS should be optimized to enhance antiarrhythmic drug therapy and reduce the risk of relapse in those patients undergoing catheter ablation.[11]

Diabetes Mellitus

Since the Framingham study,[7,8,16] diabetes mellitus (DM) is considered a risk factor for AF. There is up to a 40% increase in the risk of developing AF as a diabetic depending on age and diagnostic time. Moreover, there is a direct correlation between glycated hemoglobin levels and the incidence of AF. [50]

Patients with DM generally have other comorbidities considered to increase the risk of AF. The pathophysiology of DM, which is not yet completely elucidated, involves the presence of oxidative stress, inflammation, formation of advanced glycosylation derivatives with induction of myocardial fibrosis and hypertrophy, and the promotion of electroanatomic remodeling of the left atrium.[4,5,51]

Glycemic control with the use of metformin showed a protective role in the incidence of AF in a Taiwanese population over

13 years.[52] Other antidiabetic drugs have not been studied to date. Clinical trials to evaluate the impact of glycated hemoglobin control and prevention of AF have not yet been conducted.[52,53]

Diet

There is no evidence of a specific diet that provides clear benefits for the prevention of AF. It is believed that the Mediterranean diet can contribute to its prevention by controlling comorbidities and providing a favorable nutritional profile, rich in unsaturated fatty acids.[54,55]

One of the cohorts in the Framingham Heart study found that there is an association between hypomagnesemia and the risk of developing AF.[56] A total of 3,530 individuals without cardiovascular disease and AF (mean age of 44 years; 52% were women), were found to have an age- and gender-adjusted AF incidence rate of 9.4 per 1,000 person-years (95% confidence interval, 6.7-11.9) in the lowest quartile of serum magnesium (≤ 1.77 mg/dL) versus 6.3 per 1,000 person-years (95% confidence interval, 4.1-8.4) in the highest quartile (≥1.99 mg/dL).

Individuals in the lowest quartile had about a 50% greater risk of developing AF (adjusted risk ratio, 1.52; 95% confidence interval, 1.00-2.31; P=0.05) compared to those in the upper quartiles. The results were similar after the exclusion of individuals using diuretics.[56]

Hypomagnesemia is also associated with increased risk of developing AF over time, proportionally to its serum level; therefore, periodic evaluation and replacement is recommended if necessary.[11,22]

Obesity

Obesity is commonly accompanied by cardiometabolic comorbidities, all contributing to the AF epidemic. In the LEGACY[13] study, progressive weight loss was found to reduce AF with consequent maintenance of sinus rhythm, even without antiarrhythmic pharmacological strategies.

Reductions of more than 3% of body mass reduced the burden of AF by up to 13%, with a dose-dependent effect that reached 46% when weight was reduced by more than 10%, in addition to having other favorable effects. Weight gain and fluctuation lead to structural remodeling, higher pressure levels, higher glycemic rates, higher apnea/hypopnea rates, and higher AF loads.[3,13]

Mental Health and Psychological Stress

Experiencing psychological stress such as anxiety and/or depression is extremely common in patients with AF, affecting 25 to 50% of patients. However, these symptoms only increase the risk of developing AF in men with tension and aggressive personality traits.[57]

Depression is associated with unregulated lifestyle habits, such as smoking, excessive alcohol use, unfavorable dietary patterns, a sedentary lifestyle, poor drug adherence, and greater predisposition to other risk factors for AF. An improved mood decreases incidence of AF.[58] The practice of yoga may reduce the number of symptomatic episodes by up to 24%.[59]

Physical Activity

Current evidence shows that although physical activity recommendations for patients with heart problems are insufficient to adequately prevent AF, 3.5 hours of moderate weekly physical activity can reduce the incidence of AF by 10%.[60]

Not only the amount of physical exercise, but the maintenance of physical conditioning to perform more strenuous activities (> 8 metabolic equivalents or consumption of peak VO2 > 28 mL/kg/min.), have a favorable profile in the protection against AF.[20,60]

In older patients, it is known that leisure time (and sedentary lifestyle) is associated with lower incidence of AF, but this benefit was not observed in high intensity activities.[59] Although controversial, most studies of AF in athletes reinforce the role of endurance sports as an AF trigger. There is still no consensus on the type of sport, duration, and intensity of training considered a risk factor, since issues of genetic susceptibility should also be considered.[60]

Therapeutic Approach

A multifactorial and multidisciplinary approach for AF prevention can reduce outcomes such as hospitalization or death. The control of the large number of aggravating and triggering variables leads to a significant improvement in the patient's quality of life (Table 1).

The clinical perception of compensated patients, even if they have comorbidities, is the main objective in AF control. There is no point in treating only the AF itself if we do not seek

Table 1. Strategies for Controlling Risk Factors.

Strategies for Controlling Risk Factors and Therapeutic Objectives		
Risk factor	**Therapeutic objective**	**Comments**
Hypertension	BP <140/90	Consider ACEI, ARB, beta-blocker or aldosterone antagonist
Obesity	BMI <25 Weight loss between 5-10% if BMI >25	Avoid weight fluctuations
Diabetes	HbA_{1c}<7%	Metformin as first-line therapy
Sedentary behavior	150-200 minutes of moderate physical activity/week Aerobic exercise 90-150min/week	
OSAHS		*Screening of patients at risk* *Control with CPAP*
Alcoholism	20 g/day alcohol for men and 10 g/day alcohol for women	
Smoking	Complete cessation	
Dyslipidemia	Reduce LDL to 50% of baseline levels if > 100 mg/dL	Use statins

to treat the patient with it, as patients have multiple comorbidities posing therapeutic challenges and must change several lifestyle behaviors. Studies addressing the multidisciplinary treatment of AF have demonstrated that this approach is cost-effective, leads to lower recurrence rates and hospital readmissions, better responses to drug and interventionist therapeutic proposals, and reduces mortality.[20,61]

CONCLUSION

The role of clinicians in AF prevention involves an individualized approach for each patient, including all aspects discussed here, in order to achieve well-defined objectives and goals, make patients aware of the associated risks during the follow-up, and ideally prevent the development of AF. The more multidisciplinary and integrated this approach is, the greater the chance of preventing AF and its recurrence. It becomes clear that using isolated measures for the treatment of AF is not enough, thus measures addressing the interdependent aspects of this fascinating and multifaceted arrhythmic are required.

CONFLICTS OF INTEREST

The author declares that he has no conflicts of interest in this work.

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