Chapter 3

ATRIAL FIBRILLATION

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Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice and is associated with a high risk of morbidity and mortality. This condition is related to severe cardiovascular events, such as stroke, heart failure, peripheral embolism, and other causes of death. The pathophysiology of AF is complex and variable among patients, involving mechanisms such as reentry, electrical

and structural modification of atrial tissue, risk factors, genetic predisposition, poor dietary habits, sedentary lifestyle, alcoholism, and the multiple wavelet hypothesis as a perpetuation instrument of AF. Understanding this pathology has evolved substantially in recent decades (Kunal; Wong, 2019; Lau, Linz, and Sanders, 2019).

AF has a high prevalence and elevated morbidity and mortality, affecting approximately 33.5 million people globally. Current therapeutic techniques are effective but have high costs for the healthcare system. Therefore, it is essential to determine modifiable risk factors and implement appropriate preventive measures to improve public health and reduce healthcare system costs (Sagris *et al.*, 2022). The incidence of AF is significant, affecting about 33 million people, and is associated with increased morbidity and mortality, especially in emergency contexts. Risk factors include advanced age, preexisting cardiovascular and chronic diseases, and poor lifestyle habits such as alcoholism. This high incidence requires changes in the structuring of emergency services and the creation of public health policies focused on prevention and rapid patient care (Andersen, Andreasen, and Olesen, 2021).

The diagnosis of AF must be rapid and accurate in medical emergencies. The diagnostic approach includes clinical evaluation of risk factors, genetics, and comorbidities, in addition to complementary tests, with the electrocardiogram being the gold standard. Technological innovations, such as artificial intelligence, have promoted significant advances in the diagnosis of AF, facilitating its therapeutic management (Agewall, 2022; Hendriks *et al.*, 2021). Its treatment is based on heart rate control, reducing its load and duration, preventing thromboembolic events, and restoring sinus rhythm. The therapeutic approach is individualized, considering comorbidities, age, risk factors, and patient genetics (Hendriks et al., 2021).

Urbanization and lifestyle changes, such as inadequate diets and increased sedentary behavior, also play a significant role in the rising incidence of AF. Recent studies have shown that managing lifestyle and risk factors can reverse the progression of AF and maintain sinus rhythm. An integrated care approach has also been effective in reducing cardiovascular hospitalizations and all-cause mortality. Thus, managing risk factors such as obesity, hypertension, and obstructive sleep apnea shows significant impacts on the prevalence and incidence of the pathology. Overweight individuals have a higher risk of developing AF, and changes in weight over time can influence this risk. Comprehensive risk factor management programs have demonstrated that weight loss and improved cardiorespiratory fitness are associated with higher success rates in AF control and treatment (Hendriks *et al.*, 2021; Shamloo *et al.*, 2019).

Recent studies have focused on identifying the cellular and molecular mechanisms leading to atrial remodeling, an important underlying condition in atrial fibrillation (AF) (Lau, Linz, and Sanders, 2019). A significant example of clinical research in this field is the CABANA study (Catheter Ablation vs Antiarrhythmic Drug Therapy in Atrial Fibrillation), which compared the effectiveness of pulmonary vein isolation via catheter ablation with drug

therapy for rate and rhythm control. Although the study demonstrated a significant reduction in AF recurrence in the ablation group, it did not show an improvement in composite clinical outcomes such as mortality, stroke, bleeding, and cardiac arrest compared to the group treated with medications (Wijesurendra and Casadei, 2019).

EPIDEMIOLOGY

Atrial fibrillation (AF) is an arrhythmia whose prevalence increases with age, from less than 0.5% in individuals in their 40s to 10% in those over 80 years old (Huh; Jo, 2023). In 2016, an estimated 463 million individuals worldwide had AF (Kornej *et al.*, 2020). Recent data estimate that one in three people will develop the condition over their lifetime (Alonso, Almuwaqqat, and Chamberlain, 2021). In the United States, between 3 and 6 million people currently suffer from AF, with projections indicating that this number could reach between 6 and 16 million by 2050. In Europe, the prevalence of AF in 2010 was 9 million among individuals over 55, with a projected increase to 14 million by 2060. Over the past 50 years, according to the Framingham Heart Study, the prevalence of atrial fibrillation has tripled, with a lifetime risk estimated at about 1 in 3 for white individuals and 1 in 5 for black individuals. Additionally, the lifetime risk of AF has been estimated at about 1 in 4 white men and women over 40 years old by 2047 (Kornej *et al.*, 2020).

Several factors contribute to these changes. The aging population is one of the main factors, as the prevalence of AF increases substantially with age. Awareness and improved detection of AF have also improved in the last decade, which is crucial given that about one-third of people with AF are asymptomatic (Kornej *et al.*, 2020). In addition to age, the management of risk factors plays a crucial role. Omega-3 fatty acid supplementation, initially considered beneficial for preventing cardiovascular diseases, has shown conflicting results in human studies. Higher doses of omega-3 may increase the risk of AF, especially in individuals with high cardiovascular risk or established cardiovascular diseases (Huh; Jo, 2023). Individuals with multiple risk factors such as obesity, hypertension, diabetes, smoking, and excessive alcohol consumption have an even higher risk of developing AF. Epidemiological studies have demonstrated a strong and independent relationship between obesity and AF, with a 4% to 5% increase in the risk of incidence for each additional unit in body mass index (BMI). Hypertension is also one of the main risk factors, associated with left ventricular hypertrophy and diastolic dysfunction, pathophysiological characteristics of chronic hypertension related to the occurrence of AF. Excessive alcohol consumption and smoking also significantly increase the risk of AF (Shamloo *et al.*, 2019).

Ethnic disparities in detection and treatment, as well as the lack of primary prevention, are significant challenges for the proper management of AF. Studies have revealed that individuals of African or Hispanic descent have lower rates of AF, despite a similar or more severe comorbidity profile compared to individuals of European descent, where for every

10% increase in European genetic ancestry, there is a 13% higher risk of incident AF (Kornej *et al.*, 2020). These discrepancies can be attributed to genetic, socioeconomic, and environmental differences, as well as predisposing factors such as obesity, alcohol, and tobacco consumption that influence both the manifestation and progression of the disease (Andersen, Andreasen, and Olesen, 2021).

Additionally, diagnosing AF often represents a challenge due to the asymptomatic nature of many cases. The use of cardiac monitoring devices has been crucial for detecting AF in patients with cryptogenic stroke, as demonstrated by studies. This method revealed a significant incidence of AF after cerebrovascular events, especially in racially and ethnically diverse populations (Agewall, 2022).

Genetic aspects also influence the predisposition to AF. Genetic variants that encode structural and electrical cardiac proteins have been implicated (Healey, Roberts, and Field, 2021). Studies indicate that people of European descent have a higher risk of AF compared to individuals of African or Asian descent, suggesting that genetic factors may play an important role (Kornej *et al.*, 2020).

Mortality associated with AF has shown decreasing trends in recent decades, attributed to advances in diagnosis, prevention of thromboembolic complications, and better patient management. Oral anticoagulation, for example, has proven effective in reducing strokes and mortality among patients with AF (Alonso, Almuwaqqat, and Chamberlain, 2021).

According to studies, individuals diagnosed with AF have higher cardiovascular disease mortality compared to those without the condition. Women and men with AF showed a 90% and 50% increase in mortality rates, respectively, compared to non-carriers. Recent research indicates a gradual reduction in mortality rates thanks to advances in diagnosis, prevention of thromboembolic complications, and better patient management (Alonso, Almuwaqqat, and Chamberlain, 2021).

Understanding the risk factors associated with AF is crucial for the early identification and effective management of this arrhythmia. Age is one of the most important risk factors, with prevalence increasing substantially in individuals over 40 years old and reaching up to 10% in people over 80 years old (Huh; Jo, 2023). In addition to age, several health conditions play a crucial role, such as arterial hypertension, obesity, heart failure, sleep apnea, diabetes mellitus, coronary artery disease, and chronic kidney disease (Healey, Roberts, and Field, 2021). Smoking is also associated with an increased risk of AF (Shamloo *et al.*, 2019).

DIAGNOSIS

The diagnosis of atrial fibrillation (AF) requires a detailed medical history, physical examination, electrocardiographic evaluation, and complementary tests. The medical history should include an assessment of the patient›s symptoms and a search for factors in the

clinical history related to AF, such as hypertension, hyperthyroidism, structural heart disease (valvular diseases and ischemic disease), and alcohol use, which may be associated with the holiday heart syndrome (Joglar *et al.*, 2024).

AF is the most common sustained cardiac arrhythmia and is associated with adverse outcomes that can be partially prevented by oral anticoagulation. AF meets the World Health Organization (WHO) principles for screening, with the electrocardiogram (ECG) being an important tool for screening undiagnosed AF due to its low cost, safety, and wide acceptance. However, the ECG has a low diagnostic yield (<2%) compared to continuous monitoring through implantable cardiac monitors (ICM) or pacemakers (Extramiana; Steg, 2022).

The 12-lead electrocardiogram (ECG) is the gold standard for the diagnosis of AF. Electrocardiographic findings include irregular RR intervals, absence of P waves, and the presence of f waves (small oscillations in the baseline corresponding to disorganized electrical activity). Patients with a normal ECG at the time of evaluation but with occasional symptoms may undergo ambulatory monitoring with a 24-hour Holter to investigate paroxysmal AF, as well as implantable monitors for long-term monitoring. Electrocardiographic evaluation is also essential to identify coexisting rhythm disturbances, such as atrial arrhythmias and Wolff-Parkinson-White (WPW) syndrome (Joglar *et al.*, 2024). In hospitalized patients, continuous monitoring is crucial for the early detection of acute AF, especially when precipitated by conditions such as sepsis, respiratory failure, or postoperative cardiac surgery. The use of 12-lead ECG remains essential, but telemetry offers the advantage of allowing continuous observation of the heart rhythm (Chyou *et al.*, 2023).

The echocardiogram is essential in the investigation of patients with AF, although it is not used to diagnose the condition itself. Transthoracic echocardiography evaluates valvular function, the size and function of cardiac chambers, with a special focus on the left atrium. The left ventricular ejection fraction (LVEF) impacts decisions on the use of antiarrhythmic medications or other forms of rhythm control, such as ablation. Transesophageal echocardiography is important for investigating interatrial thrombi, especially in patients with a history of AF for more than 48 hours (Joglar *et al.*, 2024).

Techniques for panoramic mapping of cardiac electrical activity have identified two main arrhythmic mechanisms: focal ectopic activations and rotations (rotors). Focal ectopic activities indicate specific areas of the heart where abnormal electrical impulses are generated, which can trigger or perpetuate AF. Rotations are rotational reentrant circuits that maintain the arrhythmia. Studies indicate that rotors detected by phase mapping have low specificity for identifying rotating wave fronts compared to activation time mapping in high-density epicardial electrograms of AF. However, most of these rotors were located near a conduction block line (Lau, Linz, and Sanders, 2019).

Laboratory investigation is indispensable in the workup of patients with AF. Thyroid hormone levels should be measured, as thyrotoxicosis is associated with AF. Laboratory tests

can detect other medical conditions that influence therapeutic decisions, such as chronic kidney disease (CKD) and liver disease (Joglar *et al.*, 2024). The use of mobile and portable devices, such as smartwatches and smartphones with ECG applications, has revolutionized the detection of AF. The Apple Heart Study demonstrated the ability of smartwatches to identify AF episodes with high accuracy in large populations (Seshadri, 2020). Recently, a wearable ECG device in the form of a necklace (Necklace-ECG) showed high sensitivity and specificity in detecting AF, making it a promising solution for screening and diagnosis (Santala *et al.*, 2023). A study evaluated the electrogram morphology recurrence (EMR) mapping technique in 42 patients, showing high recurrence in locations near AF drivers. This innovation could improve diagnostic accuracy and understanding of AF mechanisms, although more studies are needed to confirm its clinical potential (Buch; Du, 2023).

The differential diagnosis of AF includes other supraventricular tachycardias, such as atrial flutter, which can be distinguished on the ECG by the presence of sawtooth F waves and a regular rhythm. Paroxysmal supraventricular tachycardias (PSVT) present with sudden onset and termination and a regular rhythm, while ventricular-origin tachycardias show widened QRS complexes and a regular rhythm, unlike the characteristic irregularity of AF (Joglar *et al.*, 2024).

TREATMENT

Current treatments for AF include rate controllers (beta-blockers, calcium channel blockers, cardiac glycosides), rhythm controllers (antiarrhythmics, electrical cardioversion, catheter ablation), and prevention of thromboembolic events (oral anticoagulation, including warfarin and new oral anticoagulants - NOACs) (Joglar *et al.*, 2024). The use of oral anticoagulants is crucial for patients with AF, reducing the risk of stroke and mortality. Studies show that non-adherence to treatment can significantly increase the risk of adverse events. Healthcare professionals should emphasize the importance of adherence to treatment to improve outcomes and reduce morbidity and mortality (Vitolo *et al.*., 2021).

Modifying risk factors such as obesity and obstructive sleep apnea can reduce the incidence and recurrence of AF. A reduction of at least 5% in body weight, combined with moderate exercise and a balanced diet, has proven effective in controlling AF symptoms. Additionally, the adequate treatment of obstructive sleep apnea with continuous positive airway pressure (CPAP) therapy can reduce the recurrence of AF in patients undergoing electrical cardioversion (Wingerter *et al.*, 2020).

Since the introduction of catheter ablation techniques in 1998, the number of treated patients has increased significantly. Detailed knowledge of cardiac anatomy, including the conduction system (sinoatrial node, atrioventricular node, and His-Purkinje system), is crucial for the success of these interventions. Cryoablation is an effective option for patients with AF refractory to medical treatment, demonstrating superiority over antiarrhythmics for

the initial control of paroxysmal AF (Liu *et al.*, 2023). The success of ablation depends on detailed anatomical knowledge of the cardiac conduction pathways. The sinoatrial (SA) node and the atrioventricular (AV) node play crucial roles in the heart›s electrical conduction, and their integrity must be preserved during surgical procedures. Intraoperative electrophysiological mapping helps identify and protect these nodes, minimizing risks (Cox *et al.*, 2020).

Recent studies investigate the use of ethanol infusion in the vein of Marshall to achieve local parasympathetic denervation and perimitral block. One study reported a positive primary outcome in 51.6% of patients and success in perimitral block in 80.6% (Valderrábano, 2021). This technique, associated with epicardial ablation, may improve the control of persistent AF, but still requires additional confirmation (Valderrábano, 2021).

Gene therapy emerges as a promising approach for the treatment of AF, aiming to replace or remove disease-causing genes in the myocardium. Viral vectors, such as the adeno-associated virus (AAV), are suitable for cardiac gene therapy due to their low immunogenicity and long-lasting expression. Gene therapy can target areas such as ion channels, Ca2+ handling proteins, autonomic nerve remodeling, structural remodeling, inflammatory/oxidative injuries, and apoptosis (Yoo *et al.*, 2021).

The treatment of atrial fibrillation involves a combination of pharmacological, interventional, and lifestyle modification approaches. A detailed understanding of cardiac anatomy and associated risk factors is essential for therapeutic success and complication reduction (Yoo *et al.*, 2021).

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