Chinese Medical Journal®

Atrial fibrillation: mechanism and clinical management

Zhicheng Hu, Ligang Ding, Yan Yao

Cardiac Arrhythmia Center, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100037, China.

Abstract

Atrial fibrillation (AF), the most common sustained arrhythmia, is associated with a range of symptoms, including palpitations, cognitive impairment, systemic embolism, and increased mortality. It places a significant burden on healthcare systems worldwide. Despite decades of research, the precise mechanisms underlying AF remain elusive. Current understanding suggests that factors like stretch-induced fibrosis, epicardial adipose tissue (EAT), chronic inflammation, autonomic nervous system (ANS) imbalances, and genetic mutations all play significant roles in its development. In recent years, the advent of wearable devices has revolutionized AF diagnosis, enabling timely detection and monitoring. However, balancing early diagnosis with efficient resource utilization presents new challenges for healthcare providers. AF management primarily focuses on stroke prevention and symptom alleviation. Patients at high risk of thromboembolism require anticoagulation therapy, and emerging pipeline drugs, particularly factor XI inhibitors, hold promise for achieving effective anticoagulation with reduced bleeding risks. The scope of indications for catheter ablation in AF has expanded significantly. Pulsed field ablation, as a novel energy source, shows potential for improving success rates while ensuring safety. This review integrates existing knowledge and ongoing research on AF pathophysiology and clinical management, with emphasis on diagnostic devices, next-generation anticoagulants, drugs targeting underlying mechanisms, and interventional therapies. It offers a comprehensive mosaic of AF, providing insights into its complexities.

Keywords: Atrial fibrillation; Pathophysiology; Clinical management; Wearable device; Anticoagulant

Introduction

Atrial fibrillation (AF) is a prevalent cardiac arrhythmia characterized by rapid, irregular electrical activity in the atria, often resulting in a fast, irregular ventricular rhythm.[1] AF constitutes a significant public health challenge worldwide, impacting millions of individuals.[2] Symptoms associated with AF, including palpitations, dyspnea, chest discomfort, fatigue, and dizziness, can lead to reduced quality of life and increased morbidity and mortality.

Despite extensive research, uncovering the precise mechanisms behind AF remains a formidable task.[3] Current understanding suggests that factors such as stretch-induced fibrosis, epicardial adipose tissue (EAT), chronic inflammation, autonomic nervous system (ANS) imbalances, and genetic mutations contribute significantly to AF pathogenesis.[4–7] However, no specific treatment targeting the root cause of AF is currently available.

Traditionally, electrocardiograms (ECGs) have served as the gold standard for AF diagnosis. However, they are not always readily accessible. Recent advances in wearable devices have greatly enhanced AF diagnosis by offering continuous, non-invasive heart rhythm monitoring.[8] Through machine learning algorithms, healthcare providers can now detect and diagnose AF at an earlier stage.[9] Furthermore, these devices facilitate telemedicine and virtual consultations, as patients can effortlessly share their cardiac data with healthcare professionals.[10]

The goals of AF management encompass symptom control (divided into rate control and rhythm control), reduction of thromboembolic risk, and a holistic approach to patient care. Stroke prevention, accomplished through anticoagulation therapy, is crucial, particularly for individuals at high risk of developing stroke or systemic embolism (SE).

This review synthesizes existing knowledge and ongoing research on AF pathophysiology and clinical management, with a specific focus on diagnostic devices, next-generation anticoagulants, medications targeting underlying mechanisms, and interventional therapies. It provides a comprehensive perspective on AF, shedding light on its intricate nature.

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000002906

Correspondence to: Yan Yao, Cardiac Arrhythmia Center, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, 167# Beilishi Road, Beijing 100037, China
E-Mail: ianyao@263.net.cn

Chinese Medical Journal 2023;136(22)

Received: 20-07-2023; **Online:** 01-11-2023 **Edited by:** Rongman Jia

Pathophysiology and Mechanisms

The pathogenic mechanism of AF is complex. Currently, it is believed that various factors contribute to complex alterations in the atria, ultimately leading to the development and progression of AF.

Stretch-induced fibrosis

Chronic stretching of the atrial tissue due to increased pressure or volume overload on the heart lead to atrial remodeling characterized by conduction slowing, cellular calcium overload, fibrosis, fibroblast proliferation, and modifications in collagen degradation.[4,11] Prolonged hemodynamic loading is believed to stimulate fibroblast proliferation, migration, and differentiation into myofibroblasts, which secrete extracellular matrix (ECM) proteins extensively, causing fibrotic changes that contribute to the progression of AF.[12] Fibrosis hampers the proper coupling between myocardial excitation and contraction, disturbs impulse propagation, and disrupts ECM-dependent signaling pathways. *In vivo* evidence from experimental models and patient studies supports the notion that the profibrotic effect of hemodynamic load can be attributed to the activation of fibroblasts, leading to the deposition of collagen fibers and fibrotic changes. Fibrosis disrupts the normal electrical conduction pathways within the atria, leading to slowed or blocked conduction. Meanwhile, it creates an environment facilitating the generation of abnormal electrical impulses and promotes the initiation and maintenance of AF.[13]

EAT

EAT, located closely to the heart muscle, has been associated with an increased risk of AF.[5] Electroanatomic mapping studies have confirmed larger low-voltage areas adjacent to the increased EAT volume.[14] These emerging findings highlight the importance of EAT and fatty infiltration in atrial electro-structural remodeling.[15] The detrimental effects of EAT on the atrial structure can be attributed to its paracrine actions, which lead to fibrosis or direct infiltration of fat into the nearby adjacent atrial myocardium, furthermore disturbing its structure and conduction.[16]

Inflammation

Sustained inflammation is a central mediator in atrial electrical and structural remodeling in AF, characterized by increased formation of reactive oxygen species (ROS) and upregulation of cytokines.[17] AF risk factors contribute to the formation of ROS, resulting in the impairment of myocardial energetic and electrophysiologic properties.[6] A meta-analysis of available transcriptome data and a large-scale transcriptome approach confirm the ample AF-dependent ion channel remodeling involved in the inter-related oxidative stress.[18,19] Meanwhile, a growing body of evidence indicates that inflammasome signaling in atrial cardiomyocytes causes inflammation and contributes to AF pathogenesis.[20] Among the different inflammasome complexes, the nucleotide-binding oligomerization domain (NOD)-, leucine-rich repeat (LRR)-, and pyrin domain-containing protein 3 (NLRP3) inflammasome is studied the most extensively. Its continuous activation has been proved to be associated with AF.[21] Knock-in NLRP3 mice demonstrated atrial hypertrophy, a shortened effective refractory period in the atrium, and abnormal release of calcium from the sarcoplasmic reticulum, ultimately contributing to electrophysiological changes and the progression of AF. In contrast, blocking the expression of NLRP3 prevented the development of AF.[22] Several reports have highlighted the presence of multiple small molecules that can inhibit NLRP3 signaling.[23] And specific NLRP3 inhibitors have entered clinical trials conducted.[24] However, the results from most of these trials have not been published yet.

ANS

ANS plays a critical role not only in the regulation of cardiac rhythm but also in the initiation and maintenance of AF.[25] The interaction between sympathetic and parasympathetic fibres is pivotal in both triggering and sustaining AF.[26] In some patients, AF is associated with excessive vagus nerve activity.[27] This condition is often observed in individuals with bradycardia and is characterized by the onset of AF during the night. In patients diagnosed with the vagal type of AF, there tends to be a smaller left atrium volume, improved electrical properties, and AF triggered by the pulmonary veins (PVs). Apart from pulmonary vein isolation (PVI), the ablation of ganglionated plexi is emerging as a promising therapeutic approach for treating this type of AF.[28,29] Conversely, some patients experience forms of AF triggered and sustained by the sympathetic nervous system.[30] This can occur in athletes during intense physical exertion or in individuals undergoing high levels of emotional stress. In patients with this type of AF, the substrate in the left atrium is typically more adverse, often accompanied by triggers outside the PVs and a higher likelihood of recurrence.

Genetic variant

Over the past few decades, researchers have identified more than 160 genes associated with AF.[31] The first gene linked to familial AF was *KCNQ1 S140G*, which increases susceptibility to AF. Another noteworthy discovery involves *NPPA*, responsible for encoding atrial natriuretic peptide highly expressed in the heart, which has a frameshift variant associated with a shortened effective refractory period and an increased risk of AF development. Somatic variants in the *GJA5* gene, responsible for encoding the connexin 40 protein, have also been linked to AF. However, the causative role of AF in relation to variants in other genes is yet to be proven. Moreover, the currently identified AF-related genetic loci can only account for a moderate portion of the disease risk. This suggests the need for further research into common genetic variations. Since the introduction of genome-wide association studies for AF in 2007, more than 260 single nucleotide polymorphisms in 166 loci

have been associated with AF pathogenesis. These studies have revealed both common variants in large populations and rare causative variants in families, underscoring the complexity of AF as a trait. Despite these discoveries, there remains a significant gap in translating these genetic findings into actionable molecular pathways and potential therapeutic targets. To address this challenge, researchers are now exploring the use of genetic risk scores as a promising approach to enhance risk stratification for individuals with AF.[32]

In a word, this section summarizes pharmaceuticals under investigation for targeting AF causes, as outlined in Table 1.[24,33]

Clinical Management

Diagnosis and assessment

Diagnosis

The diagnosis of AF necessitates the confirmation of rhythm abnormalities through an ECG tracing displaying AF episodes lasting at least 30 seconds.[34] In recent times, there has been a growing interest in the use of wearable devices for AF diagnosis. These devices offer continuous monitoring outside of clinical settings, enabling long-term and real-time detection of AF episodes. Additionally, wearable devices are user-friendly and non-invasive, requiring minimal user effort. The data collected by these devices can be conveniently shared with healthcare providers for analysis and decision-making. The mHealth screening to prevent strokes (mSToPS) trial evaluated the feasibility and accuracy of a smartwatch-based algorithm for irregular pulse notifications. The results indicated that individuals receiving irregular pulse notifications were more likely to be diagnosed with AF compared to those without notifications.[8] The Apple Heart Study, which included over 400,000 participants, explored the use of Apple Watches' irregular rhythm notifications as a screening tool for AF. The study demonstrated a high positive predictive value for AF diagnosis using the notification algorithm.[9] The Fitbit Heart Study, involving a total of 455,699 participants, aimed to identify undiagnosed AF in large populations using wearable devices and achieved a positive predictive value of 98.2%.[35] However, there are still some challenges and limitations associated with the use of wearable devices for AF diagnosis. Firstly, there is a concern about potential overdiagnosis of AF due to false-positive notifications, which could lead to unnecessary anxiety, increased healthcare utilization, and inappropriate treatments. Additionally, not all individuals have access to or can afford such technology, which may result in disparities in AF diagnosis. Furthermore, the advisability and practicality of widespread AF screening using wearable devices remain topics of discussion. Evaluating the cost-effectiveness of implementing population-level AF screening strategies based on wearable devices is crucial. Balancing the benefits of early AF diagnosis with considerations of resource allocation and potential drawbacks is essential.[36]

Assessment

In terms of assessment, the proposed 4S-AF scheme including four AF-related domains (stroke risk, symptom severity, severity of AF burden, and substrate severity) is currently recognized as a comprehensive framework for evaluating various aspects related to AF.[37]

The selection of appropriate anticoagulation therapy hinges on an assessment of stroke risk. To estimate the likelihood of stroke in an individual patient, several scoring systems are commonly used, with the CHA_2DS_2-VASc score being the most frequently employed.[1,38] This scoring system takes into account various clinical variables, with each letter in CHA_2DS_2-VASc representing a specific risk factor. Points are assigned as follows: congestive heart failure or left ventricular dysfunction (1 point), hypertension (1 point), aged 75 years or older (2 points), diabetes mellitus (1 point), a history of stroke or transient ischemic attack (2 points), vascular disease (1 point), aged 65–74 years (1 point), and female sex (1 point). The cumulative score classifies patients as low, moderate, or high risk for stroke, aiding healthcare

Table 1: Pharmaceuticals targeting causes of AF.[24,33]

Pharmaceutical	Mechanism	Trial phase
Nicotinamide riboside	Increase in NAD+ and NADH levels	Preclinical
L-Glutamine	Fuels TCA cycle, and reduces ROS formation and ER stress	II
Geranylgeranylacetone	Induces HSP production and reduces ROS formation	Preclinical
4-Phenylbutyrate	HDAC inhibitor	Preclinical
Tubastatin, ACY-1215	HDAC6 inhibitor	Preclinical
ABT-888	PARP1 inhibitor	Preclinical
SP600125	JNK inhibitor	Preclinical
JNKI- IX	JNK2 inhibitor	Preclinical
MCC950	NLRP3 inflammasome blocker	Preclinical

AF: Atrial fibrillation; ER: Endoplasmic Reticulum; HDAC: Histone deacetylase; HSP: Heat shock proteins; JNK: c-Jun N-Terminal Kinases; NAD: Nicotinamide adenine dinucleotide; NADH: Nicotinamide adenine dinucleotide; NLRP: Nucleotide-binding oligomerization domain (NOD)-, leucine-rich repeat (LRR)-, and pyrin domain-containing protein; PARP: Poly (ADP-ribose) polymerase; ROS: Reactive oxygen species; TCA: Tricarboxylic acid cycle.

professionals in making informed decisions about appropriate anticoagulation therapy.

Evaluating the severity of symptoms is essential for prioritizing treatment interventions and enhancing the quality of life for patients. Symptoms associated with AF can vary significantly. Some patients may remain asymptomatic, while others may experience debilitating symptoms that profoundly affect their quality of life. To assess symptom severity, healthcare professionals often rely on validated questionnaires, such as the AF-Specific Health-related Quality of Life (AF-QoL) questionnaire or the European Heart Rhythm Association (EHRA) score, which is recommended in guidelines.[1,39] The EHRA symptom score assesses the impact of AF on a patient's daily life and classifies symptoms into four grades: Grade I indicates no symptoms; Grade II represents mild and tolerable symptoms that have a minor impact on daily activities; Grade III signifies moderate symptoms that noticeably limit daily routines; and Grade IV indicates severe symptoms that prevent patients from performing regular daily activities.

Comprehending the burden of AF is instrumental in selecting appropriate therapeutic strategies, whether they involve rhythm control or rate control approaches. By evaluating the duration, frequency, and patterns of AF episodes, healthcare professionals can make informed decisions about whether rhythm control or rate control strategies are better suited for individual patients. This assessment of AF burden facilitates the development of personalized management plans, thereby optimizing treatment outcomes and enhancing patient satisfaction and quality of life.

Evaluating substrate severity offers valuable insights into the potential success of interventions, such as ablation procedures. Various diagnostic methods, including echocardiography, cardiac magnetic resonance imaging (MRI), invasive electrophysiological studies, and biomarkers, provide essential information about parameters such as left atrial size, the presence of left atrial appendage thrombus, left ventricular function, the extent of fibrosis, and conduction abnormalities. One novel biomarker of interest in the context of AF is Galectin-3, a β-galactoside-binding protein. Galectin-3 is known to play a role in inflammation, myocardial fibrosis, and angiogenesis, which can contribute to the development of re-entrant circuits associated with AF. Previous studies have demonstrated elevated levels of galectin-3 in AF patients.[40]

Integrated management

The primary goals of treating AF is to improve clinical symptoms, reduce the risk of stroke and SE, and effectively manage the associated risk factors and comorbidities in clinical practice.

Stroke prevention

Strokes associated with AF are typically more severe than non-AF-related strokes. Managing stroke prevention in AF patients involves a comprehensive approach, which includes assessing the risk of stroke, balancing it against the risk of bleeding, and determining the appropriate oral anticoagulant (OAC) therapy.[41] In some cases, left atrial appendage closure (LAAC) may be considered.

It is recommended that anticoagulants be administered when a CHA_2DS_2-VASc score of over two in men or three in women is obtained, while consideration for initiating anticoagulation therapy is advised for a score of one in men or two in women.[1] The risk of stroke is dynamic, with approximately 20% of patients initially classified as having low stroke risk transitioning into groups with medium and high stroke risk within a year. Therefore, for patients who do not initially meet the criteria for anticoagulation therapy, stroke risk should be reassessed at least annually to enable timely adjustments to the anticoagulation strategy.[42] Once the decision to initiate anticoagulation therapy is made, the prescription of OAC should be carried out promptly. OACs encompass both warfarin and non-vitamin K antagonist oral anticoagulants (NOACs). NOACs are preferred over warfarin, except for patients with mechanical heart valves or moderate-to-severe mitral stenosis who require warfarin for anticoagulation.[43] Patients taking warfarin should undergo regular monitoring of the international normalized ratio (INR) and adjust the dosage to maintain it within the therapeutic target range of 2.0 to 3.0. Clinical trials have demonstrated the non-inferiority of NOACs in terms of efficacy and safety for preventing ischemic stroke and systemic embolism in AF patients compared to warfarin, with a notable reduction in the risk of intracranial hemorrhage.[44]

A comprehensive assessment of potential bleeding risk should precede the initiation of anticoagulation therapy. Currently, the HAS-BLED bleeding score is the most widely accepted model for predicting bleeding risk.[45] The acronym "HAS-BLED" stands for hypertension, abnormal renal/liver function, stroke history, bleeding history or predisposition, labile INR, elderly, and drugs/alcohol concomitantly. Each item is assigned one point, and a HAS-BLED score of ≥3 indicates a high bleeding risk. It's important to note that while a high bleeding risk score should not be considered a contraindication for the use of OAC,[46] patients with a high bleeding score can still derive significant benefits from anticoagulation therapy.

Whether AF patients should undergo anticoagulation treatment hinges on the careful evaluation of benefits versus bleeding risks. Bleeding risk factors can be categorized as reversible (e.g., hypertension, excessive alcohol intake) and irreversible (e.g., age, prior history of hemorrhage). Identifying and addressing reversible and partially reversible risk factors are vital steps in mitigating bleeding risk. Patients on warfarin should aim to maintain their INR within the therapeutic range, while those on NOACs should have their drug choices and doses tailored to their individual needs.[47] Furthermore, it is essential for all patients to receive education on self-monitoring related to bleeding. For individuals with a

history of upper gastrointestinal bleeding, co-administration of proton pump inhibitors significantly reduces the risk of major gastrointestinal bleeding.[48] In recent years, there has been promising research on Factor XI inhibitors, which have the potential to reduce bleeding risks and enhance the safety of current OACs.[49] These drugs are anticipated to accumulate more clinical data, become available on the market soon, and offer a higher quality and more efficient treatment option for AF patients.

Some patients are unable to use anticoagulants due to contraindications. The physical removal or closure of the left atrial appendage can theoretically serve as an alternative to OACs and achieve the goal of preventing AF-related strokes without increasing the risk of bleeding. For patients eligible for OAC therapy, studies have demonstrated that LAAC is non-inferior to warfarin in preventing stroke and SE.[50] The results of the left atrial appendage closure *vs*. novel anticoagulation agents in AF (PRAGUE-17) study indicate that LAAC is not inferior to NOACs in preventing stroke, SE, major bleeding, or clinically relevant non-major bleeding events, as well as surgery-related complications.[51] Additionally, it significantly reduces clinically relevant non-major bleeding events unrelated to the procedure. However, it's important to note that the occurrence rate of severe procedure-related complications, currently at 4.5%, requires close attention. At present, major guidelines recommend LAAC for patients with contraindications to anticoagulant therapy.

Symptom control

The primary symptom of AF is palpitations. In fact, for most patients, symptom relief is achieved as long as their ventricular rate can be controlled within a certain range. Consequently, the decision between rhythm control and heart rate control strategies has remained a topic of debate.

At the beginning of the 21st century, studies failed to demonstrate that a rhythm control strategy could improve outcomes in patients with AF. However, the results of the early treatment of atrial fibrillation for stroke prevention (EAST-AFNET 4) trial, which enrolled newly diagnosed AF patients, showed a promising 21% reduction in the primary composite endpoint (including cardiovascular death, stroke, worsening heart failure, and hospitalization due to acute coronary syndrome) in the rhythm control group.[52] The key factor behind these differing outcomes lies in the advancements in rhythm control methods. This approach now involves more sophisticated techniques, more rational use of antiarrhythmic drugs (AADs), and approximately 20% of patients undergoing catheter ablation. Furthermore, there has been a notable increase in the proportion of patients receiving anticoagulation therapy and the widespread adoption of NOACs compared to earlier studies.

AADs and catheter ablation represent the primary methods for rhythm control in AF. AADs are often recommended as a first-line treatment due to their reasonable efficacy, cost-effectiveness, and widespread availability. However, it's important to note that adverse reactions related to AADs are relatively common. In line with the principle of prioritizing safety over effectiveness, individualized AAD treatment strategies should be selected based on the patient's specific condition.[1] In cases where the desired effect is not achieved or adverse reactions occur, physicians and patients should collaborate to promptly identify and switch to alternative medications.

Catheter ablation has garnered substantial research support for its effectiveness in rhythm control, demonstrating a significant reduction in the risk of AF recurrence.[53] Particularly, as a first-line treatment for paroxysmal AF, catheter ablation has shown considerable superiority over AADs in reducing symptomatic AF recurrences and improving the quality of life.[54] However, it's worth noting that the catheter ablation versus antiarrhythmic drug therapy for AF (CABANA) study did not yield positive results regarding whether catheter ablation can improve AF prognosis.[55] On the other hand, the catheter ablation *vs*. standard conventional treatment in patients with left ventricular dysfunction and AF (CASTLE-AF) study revealed that catheter ablation can significantly reduce the composite endpoint of all-cause mortality and heart failure hospitalization in patients with AF and a left ventricular ejection fraction <35% who have an implanted implantable cardioverter-defibrillator or cardiac resynchronization therapy-defibrillator.[56] Additionally, the catheter ablation for AF in patients with end-stage heart failure and eligibility for heart transplantation (CASTLE-HTx) study suggests that the combination of catheter ablation and medical therapy may lead to a reduction in the composite endpoint of death from any cause, implantation of a left ventricular assist device, or urgent heart transplantation compared to medical therapy alone.[57]

At present, PVI stands as the most commonly performed procedure for catheter ablation of AF. However, due to the less-than-ideal success rate achieved with PVI alone, many medical centers now incorporate additional ablation strategies beyond PVI.[58,59] When it comes to energy sources for ablation, both radiofrequency and cryoballoon ablation have demonstrated similar safety and effectiveness in studies where PVI was the primary ablation endpoint.[60,61] A novel and emerging energy source for ablation is pulsed field ablation (PFA), which offers theoretical advantages.[62] PFA has the potential for selective action on myocardial cells while minimizing impact on adjacent tissues. Clinical studies have indicated fewer adverse events with PFA compared to other ablation techniques. PFA has also shown promise in achieving lasting lesions and sustaining sinus rhythm in AF patients. Additionally, it has been associated with shorter procedure times and improved overall efficiency. Its simplified procedural workflow and user-friendliness could expedite physician training and the adoption of this technology. Nevertheless, ongoing research and clinical trials are necessary to further validate its advantages and real-world effectiveness.[63,64]

Surgical treatment for AF can be categorized into two main approaches: concomitant surgical treatment of AF during cardiac surgery or standalone procedures. For patients with coexisting AF who require cardiac surgery for other cardiac conditions, the consideration of concomitant surgical treatment for AF is advisable.[65] Regarding specialized surgical treatments for AF, maze surgery has demonstrated a sinus rhythm maintenance rate of approximately 90% at the 7-year mark for persistent AF.[66] As minimally invasive surgical ablation techniques for AF continue to advance, epicardial ablation performed through thoracoscopy is gaining popularity in surgical treatment. The catheter ablation versus thoracoscopic surgical ablation in long standing persistent AF (CASA-AF) study revealed no significant difference in the sinus rhythm maintenance rate after 12 months between patients with persistent AF who underwent thoracoscopic epicardial ablation and those who underwent percutaneous catheter ablation.[67] Furthermore, the convergence of epicardial and endocardial ablation for the treatment of symptomatic persistent AF (CONVERGE) study demonstrated that a combination of thoracoscopic epicardial ablation with intracardiac mapping and catheter ablation resulted in a higher sinus rhythm maintenance rate compared to percutaneous catheter ablation in patients with persistent/long-standing AF, albeit with a slightly increased risk of complications.[68]

For patients with long-standing persistent and permanent AF, when the potential benefits of maintaining sinus rhythm are outweighed by the risks or it becomes impossible to maintain sinus rhythm, a rate control approach should be pursued to alleviate patient symptoms. Studies have shown that lenient ventricular rate control (resting heart rate <110 beats/min) is non-inferior to strict ventricular rate control (resting heart rate ≤80 beats/min, heart rate during moderate exercise <110 beats/min).[69] Therefore, the initial ventricular rate control target for AF patients can be set at a resting heart rate <110 beats/min. If symptoms persist, a more stringent ventricular rate control approach can be considered. Commonly used medications for long-term ventricular rate control include beta-blockers, non-dihydropyridine calcium channel blockers, digoxin, and some AADs. If a single medication fails to achieve the target heart rate, the combined use of medications should be considered. For patients who are unable to achieve adequate ventricular rate control through medication, atrioventricular nodal ablation combined with cardiac resynchronization therapy or physiological pacing represents a reasonable choice.[70,71]

Management of risk factors and concomitant diseases

Cardiovascular risk factors, comorbidities, and unhealthy lifestyles are intricately linked to the onset and progression of AF. Vigilant management of these risk factors and comorbidities constitutes a vital component of the comprehensive management of AF.

Even moderate alcohol consumption has been associated with an increased risk of developing AF, and discontinuing alcohol intake has been shown to reduce the frequency of AF episodes and decrease their burden.[72] Additionally, alcohol consumption elevates the risk of bleeding and stroke in AF patients, whereas abstaining from alcohol is linked to a reduced recurrence rate of AF following catheter ablation.[73]

The relationship between exercise and the risk of developing AF is complex. Moderate-intensity exercise has demonstrated a preventive effect on the onset of AF, whereas athletes engaged in long-term high-intensity exercise are at a greater risk of developing AF.[74] Engaging in appropriate exercise has been associated with a reduced risk of long-term cardiovascular mortality and all-cause mortality in individuals with AF.[75]

Obesity markedly elevates the risk of stroke and mortality in individuals with AF.[76] Furthermore, it serves as a risk factor for AF recurrence following ablation procedures. Weight loss has been shown to alleviate AF-related symptoms, enhance quality of life, and lower the recurrence rate after catheter ablation.

Hypertension stands as a significant risk factor for the development of AF. The systolic blood pressure intervention (SPRINT) trial has demonstrated that intensive blood pressure lowering is associated with a reduced risk of new-onset AF. Moreover, hypertension substantially increases the risk of cardiovascular events in individuals with AF.[77] Subgroup analysis of the SPRINT study has revealed that the cardiovascular benefits of intensified blood pressure control are more pronounced in AF patients compared to non-AF patients.[78] Nevertheless, further research is needed to determine the optimal blood pressure target for individuals with AF.

Diabetes mellitus raises the risk of AF by approximately one-third and also increases the risk of stroke and mortality among AF patients.[79] Recent research suggests that sodium-glucose cotransporter-2 inhibitors (SGLT-2i) can reduce the risk of AF in diabetic patients. Furthermore, in individuals with both AF and diabetes, SGLT-2i has shown promise in lowering the risk of major cardiovascular events.[80] Recent research suggests that SGLT-2i reduce AF recurrence after catheter ablation in patients with type 2 diabetes mellitus.[81]

Conclusion

AF remains a significant healthcare challenge, with its multifaceted pathophysiology necessitating a comprehensive diagnostic and therapeutic approach. The integration of wearable devices, next-generation anticoagulants, drugs targeting underlying mechanisms, and innovative interventional therapies holds the potential to transform AF management. Research efforts should continue to unlock the mysteries surrounding AF and enhance patient outcomes.

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How to cite this article: Hu ZC, Ding LG, Yao Y. Atrial fibrillation: mechanism and clinical management. Chin Med J 2023;136:2668–2676. doi: 10.1097/CM9.0000000000002906

Corrigendum

Corrigendum: treatments for resectable esophageal cancer: from traditional systemic therapy to immunotherapy

The authors declare that in the article "Treatments for resectable esophageal cancer: from traditional systemic therapy to immunotherapy"[1] which was published in vol. 135, issue 18, page 2143–2156 of the *Chinese Medical Journal*, the affiliation of the first author Yan Yan should be corrected as "Department of Thoracic Surgery, Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China". The authors deeply apologize for any inconvenience caused.

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1. Yan Y, Feng X, Li C, Lerut T, Li H. Treatments for resectable esophageal cancer: from traditional systemic therapy to immunotherapy. Chin Med J 2022;135:2143–2156. doi: 10.1097/CM9.0000000000002371.