Journal of Biosciences and Medicines, 2024, 12, 393-401
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Research Progress of Atrial Fibrosis in Recurrence of Atrial Fibrillation

Ke Li, Jingchao Long

Department of Cardiology, Jingzhou Hospital Affiliated to Yangtze University, Jingzhou, China
Email: like199104@163.com

How to cite this paper: Li, K. and Long, J.C. (2024) Research Progress of Atrial Fibrosis in Recurrence of Atrial Fibrillation. *Journal of Biosciences and Medicines*, **12**, 393-401.
https://doi.org/10.4236/jbm.2024.1212031

Received: November 19, 2024
Accepted: December 21, 2024
Published: December 24, 2024

Abstract

Atrial fibrillation (AF) is the most common arrhythmia in clinic. With the increasing aging of the population in China, the incidence of atrial fibrillation is also increasing with age. The formation and progression of atrial fibrillation are mainly the changes of atrial anatomical structure and electrophysiological mechanism, in which atrial fibrosis plays a key role in the structural remodeling and electrical remodeling of atrial fibrillation. Although catheter ablation has been widely used in the basic treatment of atrial fibrillation, recurrence of atrial fibrillation may occur after radiofrequency ablation. The key factor of recurrence of atrial fibrillation is atrial fibrosis, so early intervention measures for early diagnosis and treatment of atrial fibrosis are helpful to reduce the recurrence rate after radiofrequency ablation. This article will comprehensively summarize the relevant studies of recurrence of atrial fibrosis after radiofrequency ablation of atrial fibrillation, in order to seek the treatment of recurrence after radiofrequency ablation of atrial fibrillation.

Keywords

Atrial Ibrosis, Atrial Fibrillation, Recurrence, Radiofrequency Ablation

1. Introduction

Atrial fibrillation is considered the most common heart disease worldwide, and the prevalence has increased by 30% over the past 20 years. With the aging of the world's population and the continuous improvement of chronic disease treatment, it is predicted that the proportion of morbidity and incidence of atrial fibrillation will continue to rise in the next 20 years, which undoubtedly brings great pressure to the society and economy [1]. Atrial remodeling is a central step in the development and progression of AF, which can be divided into electrical, structural, and autonomic aspects. Atrial fibrosis refers to the abnormal activity, growth and differentiation of fibroblasts, accompanied by excessive accumulation and production of myocardial extracellular matrix (ECM) proteins [2]. A significant pathological change of atrial fibrillation is atrial fibrosis, which is closely related to the abnormal structure and function of the heart. This process involves the electronic and structural reconstruction of atrial fibrillation, which is also the core step of atrial fibrillation. With the deepening of atrial fibrosis, the electrical characteristics of the atrium can be changed, which further increases the possibility of recurrence of atrial fibrillation. Therefore, early identification and intervention of atrial fibrosis, especially in the diagnosis and treatment of atrial fibrillation, plays a vital role in the control of the disease. According to scientific research, miRNA can affect cardiac remodeling by affecting the expression of ion channel proteins and adjusting the decomposition balance of extracellular matrix, which further demonstrates its function of accelerating and resisting atrial fibrillation. The stability and tissue specificity of miRNA make it play an important role in the study of atrial fibrosis in atrial fibrillation. Therefore, the in-depth exploration of the association between miRNA and atrial fibrosis in atrial fibrillation will provide a powerful starting point for the discovery of new prevention and treatment goals of atrial fibrillation, and provide a reference for future biomarkers and diagnostic work. To provide a new therapeutic approach to further improve the recurrence of atrial fibrillation after radiofrequency ablation [3]-[7].

2. Pathological Study of Atrial Fibrillation

The occurrence of atrial fibrillation is the combined effect of many factors, and its core feature is the disorder of atrial electrical activity. Relevant studies have confirmed that the electrical and pathological mechanisms of atrial fibrillation have been widely recognized. The development and maintenance of atrial fibrillation can not be separated from stimulating substances. Most of the stimulating elements are produced by abnormal discharges at the ostium of the pulmonary veins, which are often caused by changes in calcium homeostasis or autonomic activity. It can stimulate a series of behaviors including early afterdepolarization and delayed afterdepolarization, and these abnormal discharges can induce atrial fibrillation by cardiac electrical stimulation [8]-[13]. The origin of atrial fibrillation is atrial stroma. In particular, left atrial structural remodeling and atrial interstitial fibrosis are considered to be the main causes of arrhythmias. This has been demonstrated in many animal models of atrial fibrosis, which may lead to local conduction disorders and block, thereby increasing the risk of reentry into the circuit, which also increases the sensitivity to atrial fibrillation. In patients with lone paroxysmal atrial fibrillation, the normal heart panorama may show extensive or patchy fibrosis. Atrial tachycardia may also cause ECM accumulation. Cardiac fibrosis is the cause and result of atrial fibrillation [14].

3. Types and Effects of Atrial Fibrillation and Atrial Fibrosis

According to the theory of histopathology, atrial myocardial fibrosis can be divided into three types: reparative fibrosis, reactive fibrosis and perivascular tissue fibrosis. Reparative fibrosis is the replacement of dead cardiomyocytes by extracellular matrix and fibrotic fibroblasts, which affects the structure of myocardial bundles and also disrupts the transmission of electrical current. Reactive fibrosis is due to the abnormal accumulation of extracellular matrix caused by the expansion of the endomysium and perimuscular tissue, while perivascular fibrosis is due to the expansion of the microvascular adventitia. Both types of fibrosis may be the product of a long-term fibrotic stimulus that does not completely alter the architecture of the cardiac fascicles [15]. Reactive and reparative fibrosis may coexist in the left ventricle in patients with atrial fibrillation. The essence of fibrosis is the accumulation and change of ECM, and the core link of this process is to awaken the fibroblasts in the myocardium and make them become myofibroblasts. The function of myofibroblasts is to increase the accumulation of ECM and reduce the decomposition of ECM, thus causing fibrosis. ECM is a non-cellular component of the heart, which contains a variety of matrix proteins. Among these proteins, the content of proprotein is the highest in all proteins, and it accounts for 80% of the total ECM. Within these categories, the collagen content of types I and III is the most closely associated with fibrosis. The occurrence of fibrosis is triggered by a variety of factors and produce interactive effects. At the same time, atrial fibrillation itself can also trigger a variety of signal transduction pathways involved in the formation of cardiac fibrosis. Current scientific findings suggest that the main drivers of cardiac fibrosis are the renin-angiotensin-aldosterone system (RAAS), PI3K/Akt, and MAPK signaling pathways. And the signal transduction pathway of nuclear transcription factor-κB. The central mediators of atrial fibrillation include inflammation and oxidative stress, which can exacerbate cardiac remodeling and promote the occurrence of atrial fibrillation. After the heart is damaged, the number of inflammatory signaling molecules rises sharply, among which monocytes and macrophages are the main sources of inflammatory factors, and they produce a large number of pro-inflammatory substances. These inflammatory cytokines are capable of co-acting with the previously described means of stimulating fibrosis [16].

4. Atrial Fibrosis Markers Influencing Recurrence of Atrial Fibrillation

The existence of atrial fibrillation can promote atrial remodeling, lead to and maintain the occurrence and progress of atrial fibrillation, forming a vicious circle. Therefore, early diagnosis and intervention of atrial fibrosis is the key to reduce the recurrence of atrial fibrillation. The main impact indicators are as follows:

4.1. Hematological Indices

Blood tests are common and easy to perform in clinical practice, and they can predict the recurrence of atrial fibrillation with a variety of other indicators. Current medical studies have confirmed that inflammatory response has an important impact on the formation and development of atrial fibrillation and atrial fibrosis. Circulating indicators of inflammation, such as CRP and IL-6, can serve as biomarkers of AF onset and AF recurrence after radiofrequency ablation. Over the past few years, clinical research has continued to make significant progress and deepening, and several new blood markers have been found, which are closely related to the recurrence of atrial fibrillation. Sst2 can participate in atrial fibrosis and remodeling through inflammation-related pathways, and can also reveal the severity of fibrosis [17]. Studies have shown that sST2 levels are more prominent in patients with sST2 than in patients without recurrence, and that the likelihood of recurrence of atrial fibrillation increases by about 7% for every percentage point increase in sST2. LPS was significantly associated with IL-6 and hs-CRP and independently predicted AF recurrence after surgery. Epicardial adipose tissue (EAT) can actively produce adipokines and a variety of proinflammatory cytokines, which are involved in the treatment of atrial fibrillation. Among them, C1q tumor necrosis factor-related protein 3 (CTRP3) and fatty acid binding protein 4 (fatty acid binding tissue) are two important participants. FABP4) is an effective predictor of AF recurrence after ablation [18].

4.2. Indexes Related to Left Atrium

When the pressure on the atrium exceeds/or exceeds its capacity, it will be affected by inflammation, oxidative stress and harmful metabolites, which will trigger the adjustment of atrial structure, which can trigger the adjustment of atrial structure and electrical adjustment, thus triggering atrial fibrillation. The structural adjustment of the left ventricle is mainly caused by the growth of interstitial fibrosis, which will affect the structure of the heart, and this effect will be reflected in the enlargement of the left ventricle. LA fibrosis is the basis of the formation and maintenance of AF, and its recurrence rate is closely related to AF after ablation. LVA not only reflects the electrical changes of left ventricular structure, but also symbolizes fibrosis. Patient age, long-term AF status, and large left ventricular volume predicted the presence of LVA, the study showed. In a follow-up study of 147 patients with paroxysmal atrial fibrillation, Benjamin observed that patients with LVA were more likely to reoccur after multiple radiofrequency ablation procedures than patients without LVA, confirming that there is a single link between LVA and the reoccurrence of atrial fibrillation. Several academic studies have confirmed that the size and shape of the left ventricle are important parameters for predicting the recurrence of atrial fibrillation after surgery. With the corresponding parameters of the left ventricle, we can make a personalized diagnosis of the patient's condition, such as predicting the location and size of the LVA before surgery, which can help to determine the best surgical method and reduce the risk of recurrence after surgery [19].

4.3. Parameters Related to ECG

Electrocardiogram (ECG) is a non-invasive, non-interventional, and widely accepted medical cardiac diagnostic method, which is characterized by the ability to identify indices reflecting electroanatomical abnormalities that may predict the occurrence and recurrence of atrial fibrillation in advance, but has not yet been fully used in medical practice. P waves represent the operation of the atrium on the electrocardiogram, representing the initiation and transmission of atrial electrical activity. Increased P-wave duration (PWD) is strongly associated with atrial fibrosis in patients with heart disease [20].

4.4. miRNA and Atrial Fibrosis

The relationship between miRNA and atrial fibrosis in atrial fibrillation miRNA is a single-stranded non-protein-coding ribonucleic acid with a length of 15 to 23 nucleotides. MiRNAs can also associate with the 3'UTR and CDS of mRNA, thus affecting almost all pathological and biological processes. Inhibition of messenger RNA and breakdown of mRNA, as well as 3'UTR and CDS ligation, can negatively affect not only gene expression, but also most diseases and physiological processes. Past scientific exploration has revealed the role of miRNA in the regulation of myocardial self-contraction, ion channel activity and other cardiac functions. Recent studies have found that the expression of miRNA can be transformed in both animal models and patients with atrial fibrillation. The increase or decrease of miRNA will affect the sensitivity to atrial fibrillation, so the regulation of abnormal miRNA is of key significance for treatment [21]. Although atrial fibrillation (AF) is a common continuous arrhythmia in clinical practice, its diagnosis is full of challenges because of its manifestations of paroxysmal atrial fibrillation, asymptomatic atrial fibrillation and subclinical atrial fibrillation. Biomarkers are particularly critical in medical diagnosis, given that traditional electrocardiography is not effective in identifying atrial fibrillation. In recent years, many miRNAs have been successfully used as a possible biomarker to predict the prognosis of atrial fibrillation. See **Table 1** for details.

Table 1. miRNA as a biomarker for AF diagnosis.

miRNA	Organization Source	Target	Direction of regulation on target genes
hsa-miR-21	Plasma/Atrium	TGF-β, MMP9, STAT3, WWP-1	Down-regulated (plasma) up-regulated (tissue)
hsa-miR-29s	Plasma	FBN, ColI, ColIII	Downward adjustment
hsa-miR-125a	Plasma	IL-6R	Downward adjustment
miR-126	Serum	EGFL7	Downward adjustment
miR-133a	Plasma	KCNH2, KCNQ1, HCN2, HCN4, TGF-β1	Downward adjustment

Continued

hsa-miR-133bhsa-miR-328hsa-miR-499	Plasma	SMAD7, FASLG	Up
hsa-miR-142-5phsa-miR-223-3p	Exosomes		
hsa-miR-155-5phsa-miR-24-3p	Atrium	eNOS	Up
has-miR-483-5p	Exosomes		
hsa-miR-199a	Atrium	SIRT1	Downward adjustment
hsa-miR-409	Plasma	SMAD2, ITGB3, ACE, CDKN2B	Downward adjustment
hsa-miR-432	Plasma		

4.5. microRNA and the Treatment of Atrial Fibrillation

At present, the mainstream treatment of atrial fibrillation includes drug therapy, radiofrequency ablation, left atrial appendage occlusion and other treatments, but due to the poor efficacy of drugs, side effects of drugs and surgical sequelae, the effect of these treatments has not yet reached clinical expectations. In recent years, with the deepening study of the molecular mechanism of atrial fibrosis morbidity, miRNA is expected to become a new target for the treatment of atrial fibrillation. See Table 2 for details.

Table 2. miRNAs are potential therapeutic targets for atrial fibrillation.

miRNA	Organization Source	Target	Direction of regulation on target genes
rno-miR-10a	Atrium	TGF-β1, α-SMA, Smads	Up
hsa-miR-23-b-3phsa-miR-27b-3p	Atrium	TGF-βR3	Up
mmu-miR-27b-3p	Atrium	ALK5, Cx40	Up
rno-miR-28b	Atrium	ERK	Up
mmu-miR-29b	Atrium	TGF-βR3	Downward adjustment
ocu-miR-30a	Atrium	Snail1	Downward adjustment
mmu-miR-133ammu-miR-133b	Atrium	Wnt/calciumTGF-β1	Downward adjustment
cnf-miR-133cnf-miR-590	Plasma	TGF-βR2	Downward adjustment
mmu-miR-206	Atrium	Cx43	Up

5. Summary and Outlook

With the aging of the population in China becoming more and more serious, the proportion of morbidity with atrial fibrillation is increasing every year. Catheter ablation of atrial fibrillation has become the main treatment for patients with atrial fibrillation, but the risk of recurrence is also increasing [22]. In the early phase of AF, left atrial remodeling is mainly reflected in the changes of electrophysiology and ion channels, which is called electrical remodeling. Then, with the development of time, it will lead to fibrosis of atrial muscle and extracellular matrix, amyloid changes, cell death and other structural changes, resulting in structural remodeling, and finally lead to interstitial fibrosis and left atrial expansion. Therefore, it is critical to effectively identify the severity of left atrial fibrosis, while working to minimize the recurrence of AF after catheter ablation, so as to minimize its recurrence [23]. The expression of miRNA has obvious tissue or cell specificity *in vivo*, can stably exist in serum or plasma, and can be easily obtained. Therefore, miRNA may become a new biomarker of AF, which can help to evaluate the risk and treatment effect of AF. In addition, miRNA may be a therapeutic target for atrial fibrillation. However, due to the wide spectrum of genes and miRNAs involved in AF fibrosis, and the precise and complex regulation of miRNAs, the exploration of such biological regulatory networks has not yet reached sufficient depth and integrity. Therefore, how to manage the side effects of miRNA on multiple targets, that is, to enhance the targeting specificity of miRNA, is a research problem that needs to be urgently dealt with. We firmly believe that with the comprehensive, systematic and in-depth study of miRNAs related to AF, the ideal of preventing, reversing and treating AF through precise regulation of miRNAs will eventually become a reality [24]. Therefore, it is necessary to explore the mechanism of atrial fibrillation more deeply. Accurate prediction of the various effects that may cause AF recurrence after surgery will identify potential risks early in the actual medical procedure and implement necessary protective strategies.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Wang, P.P., Liu, Y.H. and Chen, C. (2020) Research Progress on the Improvement of Myocardial Fibrosis Matrix in the Left Atrium. *Advances in Cardiology*, **41**, 1192-1195.

[2] Liang, Y.M. and He, Z. (2019) Research Progress on the Mechanism of Atrial Fibrillation Induced by Transforming Growth Factor Β/Smad Signaling Pathway. *Journal of Practical Cardio-Cerebro-Pulmonary Vascular Diseases*, **27**, 117-120.

[3] Lippi, G., Sanchis-Gomar, F. and Cervellin, G. (2020) Global Epidemiology of Atrial Fibrillation: An Increasing Epidemic and Public Health Challenge. *International Journal of Stroke*, **16**, 217-221. https://doi.org/10.1177/1747493019897870

[4] Chen, B. and Frangogiannis, N.G. (2020) Chemokines in Myocardial Infarction. *Journal of Cardiovascular Translational Research*, **14**, 35-52. https://doi.org/10.1007/s12265-020-10006-7

[5] Jiang, Y.Y., Wang, K. and Shi, C. (2018) Research Progress of Atrial Fibrillation Caused by Myocardial Fibrosis. *Medical Information*, **31**, 28-30.

[6] Staerk, L., Sherer, J.A., Ko, D., Benjamin, E.J. and Helm, R.H. (2017) Atrial Fibrillation. *Circulation Research*, **120**, 1501-1517. https://doi.org/10.1161/circresaha.117.309732

[7] López-Canoa, J.N., Couselo-Seijas, M., González-Ferrero, T., Almengló, C., Álvarez,

E., González-Maestro, A., *et al*. (2022) The Role of Fatty Acid-Binding Protein 4 in the Characterization of Atrial Fibrillation and the Prediction of Outcomes after Catheter Ablation. *International Journal of Molecular Sciences*, **23**, Article 11107. https://doi.org/10.3390/ijms231911107

[8] Wang, M., Xiong, H., Lu, L., Zhu, T. and Jiang, H. (2022) Serum Lipopolysaccharide Is Associated with the Recurrence of Atrial Fibrillation after Radiofrequency Ablation by Increasing Systemic Inflammation and Atrial Fibrosis. *Oxidative Medicine and Cellular Longevity*, **2022**, Article ID: 2405972. https://doi.org/10.1155/2022/2405972

[9] Kwan, E., Ghafoori, E., Good, W., Regouski, M., Moon, B., Fish, J.M., *et al*. (2024) Diffuse Functional and Structural Abnormalities in Fibrosis: Potential Structural Basis for Sustaining Atrial Fibrillation. *Heart Rhythm*. https://doi.org/10.1016/j.hrthm.2024.10.060

[10] Gonzalo, A., Augustin, C.M., Bifulco, S.F., Telle, Å., Chahine, Y., Kassar, A., *et al*. (2024) Multiphysics Simulations Reveal Haemodynamic Impacts of Patient-Derived Fibrosis-Related Changes in Left Atrial Tissue Mechanics. *The Journal of Physiology*. https://doi.org/10.1113/jp287011

[11] Schotten, U., Goette, A. and Verheule, S. (2024) Translation of Pathophysiological Mechanisms of Atrial Fibrosis into New Diagnostic and Therapeutic Approaches. *Nature Reviews Cardiology*. https://doi.org/10.1038/s41569-024-01088-w

[12] Skoda, I., Henningsson, M., Karlsson, L.O. and Carlhäll, C. (2024) The Spatial Overlap between Left Atrial Epicardial Adipose Tissue and Fibrosis Is Not Associated to Clinical Stage of Atrial Fibrillation. *Scientific Reports*, **14**, Article No. 24885. https://doi.org/10.1038/s41598-024-75428-8

[13] Xue, Y.C. (2024) Diagnostic Value and Clinical Significance of miRNA-320c in Atrial Fibrosis of Patients with Atrial Fibrillation. Anhui Medical University.

[14] Li, H.L. (2023) Protective Effect and Mechanism of SIRT1/GCH1/Nrf2 Pathway in Atrial Fibrosis of Atrial Fibrillation Induced by High Fat. Shandong University.

[15] Zhu, P.J. (2023) MicroRNA Sequencing Analysis of Plasma Exosomes in Patients with Atrial Fibrillation: miR-124-3p Regulates Target Gene AXIN1 to Promote Atrial Fibrosis. Shandong University.

[16] Miao, L.N. (2024) Analysis of Prognostic Factors of Patients with Atrial Fibrillation and Mechanism Study of Maixuekang Enteric-Coated Tablets Against Atrial Fibrosis. Beijing University of Traditional Chinese Medicine.

[17] Ning, J.X., Ye, N., Wang, G.Q., Bian, W.J. and Cheng, H. (2024) Research Progress on Safety of Antithrombotic Therapy in Patients with Chronic Kidney Disease and Atrial Fibrillation after percutaneous Coronary Intervention. *Journal of Clinical Nephrology*, **24**, 772-775.

[18] Chen, R.X., Han, Y.H., Zhao, J.D., Li, B.Q. and Pu, Z.K. (2024) Study on the Influencing Factors of New-Onset Atrial Fibrillation in Patients with ST-Segment Elevation Myocardial Infarction after PCI. *Journal of Chengdu Medical College*, **19**, 861-863+867.

[19] Hong, X., Zhang, N.N. and Xu, G.D. (2024) Research Progress of Left Atrial Fibrosis in Recurrence of Atrial Fibrillation after Catheter Ablation. *Journal of Nanjing Medical University* (*Natural Science Edition*), **44**, 1165-1173.

[20] Li, X.J., Cheng, X.F. and Wei, F.Q. (2024) Serum Levels of ST2 and PI3K in Patients with Persistent Atrial Fibrillation and Their Relationship with Left Atrial Fibrosis. *Shenzhen Journal of Integrated Traditional Chinese and Western Medicine*, **34**, 80-83, 141.

[21] Liu, H.H., Qian, L.L. and Wang, R.X. (2024) Role and Mechanism of Polo-Like Kinase

2 in the Development of Atrial Fibrillation. *Chinese Journal of Cardiac Pacing and Electrophysiology*, **38**, 193-196.

[22] Gao, P., Xie, B.X., Zhou, Z.D. and Liu, T. (2024) Promoting Effect of Circulating FGF23 on Atrial Fibrosis in Chronic Kidney Disease. *Tianjin Medical Journal*, 52, 917-923.

[23] Da, Y.X., Di, N.N., Zhou, S., Cui, Z.C. and Huang, L.F. (2024) Study on the Abnormal Expression of IGFBP7 and CaN in Predicting the Degree of Left Atrial Fibrosis and Deformation Function in Patients with Ejection-Preserving Heart Failure and Atrial Fibrillation. *Chinese Journal of Cardiovascular Research*, **22**, 422-427.

[24] Shao, B.X. and Chen, L.H. (2024) Research Progress on the Correlation between Homocysteine and Atrial Fibrillation. *Modern Medicine and Health*, **40**, 1377-1382.