International Journal of Biomedicine 10(3) (2020) 198-205
http://dx.doi.org/10.21103/Article10(3)_RA3

REVIEW ARTICLE

INTERNATIONAL JOURNAL OF BIOMEDICINE

MicroRNAs in Atrial Fibrillation: Pathophysiological Aspects and Potential Biomarkers

Aleksey M. Chaulin, MD[1,2*]; Dmitriy V. Duplyakov, PhD, ScD[1,2]

[1]Samara State Medical University
[2]Samara Regional Clinical Cardiology Dispensary
Samara, the Russian Federation

Abstract

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia associated with increased morbidity and mortality. The pathophysiological mechanisms underlying the development of AF are not entirely clear. In addition, there are no optimal biomarkers for the early detection and prognosis for patients with AF. Emerging studies have uncovered a role for miRNAs in the initiation and maintenance of cardiovascular disease.This review discusses the role of miRNAs in the pathogenesis of AF as well as the possibility of using miRNAs as biomarkers for detecting and predicting AF. (**International Journal of Biomedicine. 2020;10(3):198-205.**)

Key Words: atrial fibrillation • microRNA • pathophysiology • biomarker

Abbreviations

AF, atrial fibrillation; **ANS**, autonomic nervous system; **CAF**, chronic AF; **CHD**, coronary heart disease; **CVD**, cardiovascular disease; **CHF**, congestive heart failure; **ER**, electrical remodeling; **HF**, heart failure; **LAA**, left atrial appendage; **LTCC**, L-type calcium channel; **LA**, left atria; **miRNA**, microRNA; **c-miRNA**, circulating miRNA; **RAA**, right atrial appendage; **SR**, structural remodeling.

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. According to the latest data, there are more than 33 million people suffering from AF in the world, and gender-specific morbidity has been observed. In men, the incidence of AF is 3 times higher than in women.[1] Many genetic, molecular, and environmental risk factors associated with AF are also major risk factors for morbidity and mortality among patients with cardiovascular disease (CVD).[2]

The simplest and most frequently used method for diagnosing AF is electrocardiography, but this method has a significant drawback, which consists in the short duration of recording the electrical activity of the heart, which limits the diagnosis in asymptomatic patients.[3] Existing laboratory biomarkers of myocardial damage (cardiac troponins, natriuretic peptides, creatine phosphokinase, lactate dehydrogenase, aspartate aminotransferase, etc.), among which cardiac troponins are most sensitive and specific,[4,5] are not very effective for detecting and predicting AF.[6] The elevation in troponin levels occurs because of a mismatch between oxygen demand and supply. The escalated heart rate increases myocardial oxygen demand while decreasing myocardial oxygen supply by shortening diastolic time.[6,7] The shortened diastolic phase reduces the time for myocardial perfusion, a majority of which occurs during diastole. According to some reports, troponins correlate well with the severity of arrhythmias and can be used as prognostic markers,[8] but according to other sources, they are ineffective as biomarkers.[9] Therefore, there is a need to search for new and reliable biomarkers for the early diagnosis of AF.

Heart failure (HF), diabetes, hypertension, hyperthyroidism, obesity, gender, and structural and ischemic heart diseases are the most common risk factors associated with AF.[10] The genetic component was recently also considered as a significant risk factor for AF.[11,12]

miRNAs are endogenous 21–22-nucleotide noncoding small RNAs that regulate physiological and disease processes at the post-transcriptional level. The first such tiny regulatory RNA

***Corresponding author:** Aleksey M. Chaulin, MD. Samara State Medical University; Samara Russia. E-mail: alekseymichailovich22976@gmail.com*

to be identified was the lin-4 RNA, which controls the timing of *Caenorhabditis elegans* larval development.[13] Over the last few years, miRNAs have been the focus of many studies, providing evidence that these small RNAs have a significant role in the modification of numerous biological pathways.[14] miRNAs regulate approximately 30% of all protein-coding genes and have therefore been predicted to be involved in almost all cellular processes.[15] miRNAs have been implicated in various human diseases like cancer,[16-18] CVD, [19-21] neurological diseases, [22,23] autoimmune diseases,[24-26] and asthma.[27,28]

miRNA regulation in CVD was first described in 2006, when specific miRNAs were found to be up- or downregulated in mouse models of cardiac hypertrophy and HF.[29] Later, it was demonstrated that AF is associated with altered miRNA levels in atrial tissue and plasma.[30,31] The regulatory function of specific miRNAs has been studied in the structural and electrical remodeling of the heart.[32-36] A number of studies have shown that c-miRNAs associated with AF could serve as potential biomarkers of the disease, whereas specific tissue miRNAs could become targets for therapy.[37-38]

According to the latest data, miRNAs play a leading role in the pathophysiology of AF, regulating mechanisms of atrial remodeling. The reduced or increased expression of miRNAs is genetically programmed and under normal conditions contributes to the development of the cardiovascular system in humans and animals.[39] At the same time, a change in the level of miRNA expression in circulating blood and tissues can occur under pathological conditions associated with the development of various CVDs, including AF, which lead to myocardial remodeling. Numerous experimental and clinical studies found the role that miRNAs play in the pathogenesis of AF. The following main pathogenetic links in the initiation and progression of AF can be distinguished, in the regulation of which microRNA is involved: electrical remodeling (ER), structural remodeling (SR), remodeling of ANS, and dysregulation of calcium levels. A discussion of the involvement of miRNAs in each of these mechanisms is presented in the main part of this article.

Electrical remodeling in AF mediated by miRNAs

ER is the most common change associated with AF. ER occurs due to decreasing L-type calcium channel conductance (ICaL) and increasing inwardly rectifying potassium conductance (IK1). Changes in the electrical properties of Ca2+-dependent potassium channels and *connexin* channels also cause AF-related ER.[40] In the process of ER, several miRNAs are involved: miRNA-1, miRNA-328 and miRNA-499, each of which exhibits several specific properties.

miRNA-1

miRNA-1 is abundantly expressed in the myocardium and plays an important role in the development of the heart and electrical activity. Dysregulation in miRNA-1 expression leads to myocardial hypertrophy, myocyte proliferation, and cardiac arrhythmias. In addition, the arrhythmogenic potential of miRNA-1 is associated with CHD.[41] A study on a rabbit model of atrial tachycardia showed that overexpression of miRNA-1 shortens the atrial refractory period induced by tachycardia and increases inward-rectifier current activity (IKs) by reducing the expression of the *KCNE1* and *KCNB2* genes encoding the potassium channel subunits. miRNA-1 knockdown, in contrast, weakened the suppression of the *KCNE1* and *KCNB2* genes, resulting in a shortening of the atrial effective period and an increase in IKs. Thus, it was found that *KCNE1* and *KCNB2* are target genes for miRNA-1. It has also been suggested that targeted suppression of these potassium channel genes enhances the duration and frequency of AF.

Jia et al.[42] showed the critical role of miRNA-1 in atrial ER and the clinical importance of miRNA-1 as a therapeutic agent in AF. Tsoporis et al.[43] studied the expression of the muscle-specific miRNA-1 and miRNA-133A in RAA biopsies and blood plasma taken before aortic cross-clamping and after reperfusion. There was no change in tissue or plasma miRNA-1 and miRNA-133A levels compared to pre CABG. However, in patients who postoperatively developed AF, compared to patients who remained in sinus rhythm, tissue miRNA-1 increased whereas miRNA-133A decreased and negatively correlated with RAA apoptosis. In postoperative AF, differential regulation of pro- and anti-apoptotic miRNAs-1 and -133A respectively in the RAA, may contribute to postoperative apoptosis. These results provide new insights into molecular mechanisms of postoperative AF with potential therapeutic implications.

As is known, miRNA-1 and miRNA-133 regulate the expression of multiple genes involved in myocardial function, including hyperpolarization-activated cyclic nucleotide-gated (HCN) cation channels. In the study performed by Yao-Dong Li et al.,[44] aged patients with AF, compared with aged patients with sinus rhythm, exhibited significantly higher HCN2 and HCN4 channel mRNA and protein expression levels ($P<0.05$), but significantly lower expression levels of miRNA-1 and miRNA-133 ($P<0.05$). Expression levels of HCN2 and HCN4 increased with age, and a greater increase was identified in patients with age−associated atrial fibrillation compared with that in those with aged sinus rhythm. These electrophysiological changes may contribute to the induction of ectopic premature beats that trigger AF. In patients with AF, miRNA-1 levels are greatly reduced, possibly contributing to up-regulation of Kir2.1 subunits, leading to increased IK1. Because up-regulation of inward-rectifier currents is important for AF maintenance, these results provide potential new insights into molecular mechanisms of AF with potential therapeutic implications.[45]

Numerous studies have confirmed the relationship between the changes in expression profile of c-miRNAs and the regulatory effect of AF-related miRNAs on ion channels. The results obtained by Yingmin Lu et al.[46] indicated that transfected miRNA-1 could significantly inhibit the expression of CACNB2 protein. miRNA-1 can decrease the intracellular Ca(2+) concentration and prevent the AF. In addition, the recently proposed involvement of miRNA-1 in the modulation of Ca2+ handling proteins, including calmodulin, phospholamban, Na+/Ca2+ exchanger (NCX), sorcin, junctin, triadin, eventually resulting in shortened refractoriness of sarcoplasmic reticulum Ca2+ release further support the hypothesis of a pivotal functional role of miRNA-1 in the pathogenesis of AF.[47]

miRNA-328

miRNA-328 contributes to adverse atrial ER in AF through targeting L-type Ca(2+) channel genes. A potential role

for miRNA regulation of cardiac depolarization was identified when Lu et al.[48] utilized computational prediction algorithms to identify CACNA1C and CACNB1 as potential targets for miRNA-328. Overexpression of miRNA-328 in experimental models recapitulated the phenotypes of AF, exemplified by enhanced AF vulnerability, diminished L-type Ca2+current, and shortened potential duration of atrial action. *CACNA1C* and *CACNB1* were established as the cognate target genes for miRNA-328 by western blot and luciferase activity assay, showing the reciprocal relationship between the levels of miRNA-328 and ICaL channel protein subunits.[48,49] Soeki et al.[50] found that plasma levels of miRNA-328 were higher in AF patients than in control subjects. Plasma miRNA-328 levels were significantly higher in the LAA than in the periphery and PV in patients with AF, but not in control subjects. The authors concluded that local production of miRNA-328 in the LA may be involved in the process of atrial remodeling in AF patients.

miRNA-499

Recently, *KCNN3*, the gene that encodes the small-conductance, calcium-activated potassium channel 3 (SK3), was found to be strongly associated with AF. The study performed by Ling et al. showed that in patients with permanent AF, atrial miRNA-499 was significantly upregulated, leading to SK3 downregulation through effects on the *KCNN3* gene expression and possibly contributing to ER in AF.[51] In addition, upregulation of atrial miRNA-499 induced the downregulation of CACNB2 (an important subunit of the LTCC) expression and may contribute to ER in AF.[52] Increased expression of miRNA-499 (2.3-fold) was observed in patients with acute new-onset AF, compared with well-controlled AF and control patients.[53]

Structural remodeling in AF mediated by miRNAs

miRNAs that participate in sarcoplasmic reticulum regulate the genes encoding the proteins responsible for the formation of the extracellular matrix and contribute to atrial fibrosis by regulating pro- and antifibrotic signaling pathways.[54] These miRNAs are mainly involved in a decrease in the conduction rate and an increase in the reentrant activity.[55] The following miRNAs participate in SR of the heart in AF: miRNA-21, miRNA-29, miRNA-126, miRNA-150, and miRNA-483.

miRNA-21

Barana et al.[56] reported that chronic AF (CAF) increases miRNA-21 expression in enzymatically isolated human atrial myocytes. Moreover, it decreases ICaL density by downregulating the expression of Ca(2+) channel subunits (CACNA1C and CACNB2). These results suggest that miRAN21 could participate in the CAF-induced ICaL downregulation and in shortening the duration of the action potential that maintains the arrhythmia.

Atrial fibrosis is the most important substrate of AF. In a study performed by Adam et al.,[57] LA from patients with AF showed a 2.5-fold increased expression of miRNA-21, compared to matched LA of patients in sinus rhythm. Increased miRNA-21 expression correlated positively with atrial collagen content and was associated with a reduced protein expression of Spry1 and increased expression of connective tissue growth factor, lysyl oxidase and Rac1-GTPase.[57]

Thum et al.[58] showed that miRNA-21 regulates the ERK-MAP kinase signaling pathway in cardiac fibroblasts, which impacts global cardiac structure and function. In vivo silencing of miRNA-21 by a specific antagomir in a mouse pressure-overload-induced disease model reduces cardiac ERK-MAP kinase activity, inhibits interstitial fibrosis and attenuates cardiac dysfunction.

The PTEN/PI3K signaling pathway was involved in a variety of physiological activities, including cell proliferation, differentiation, and apoptosis, which participate in the pathophysiology of various diseases.[59] The target genes of miRNA-21, namely, *PTEN*, are PI3K signaling pathway inhibitors. Overexpression of miRNA-21 decreased expressions of *PTEN*, thereby activating the PI3K signaling pathway, which may play a crucial role in initiation and maintenance of atrial SR.[60]

miRNA-29

The human miRNA-29 family of mirnas has three mature members, miRNA-29a, miRNA-29b, and miRNA-29c. miRNA-29s directly target at least genes related to the extracellular matrix. These genes code for several of the key proteins involved in the physiological or pathological formation of extracellular matrix. The regulation of the extracellular matrix by miRNA-29s has been implicated in the development of fibrosis in many organs, including the heart.[61] Strong antifibrotic effects of miRNA-29s have been demonstrated in the heart, kidney, and other organs.[62] Expression of miRNA-29b extracellular matrix target genes collagen-1A1(*COL1A1*), collagen-3A1 (*COL3A1*), and fibrillin increased significantly in CHF fibroblasts. miRNA-29b plasma levels were decreased in patients with CHF or AF (by 53% and 54%, respectively; both $P<0.001$) and were further decreased in patients with both AF and CHF (by 84%; $P<0.001$). miRNA-29b expression was also reduced in the atria of CAF patients (by 54% versus sinus rhythm; $P<0.05$). Adeno-associated virus-mediated knockdown of miRNA29b in mice significantly increased atrial COL1A1 mRNA expression and cardiac tissue collagen content. miRNA-29 likely plays a role in atrial fibrotic remodeling and may have value as a biomarker and/or therapeutic target.[63]

miRNA-126

miRNA-126 plays an active role in angiogenesis by regulating the expression of Epidermal Growth Factor Like-domain 7 (EGFL7). EGFL7 has been identified as a potential miRNA-126 target. EGFL7 and its specific miRNA-126 may be involved in the pathogenesis of vasculopathy and fibrosis.[64] In a study by Wei et al.,[65] relative miRNA-126 expression was downregulated in patients with AF and/or HF compared with controls. Moreover, miRNA-126 expression was markedly lower in the HF-AF group compared with the AF and HF groups. Multiple linear regression analysis showed that miRNA-126 expression was positively correlated with LVEF, but negatively correlated with the logarithm of NT-pro BNP and the cardiothoracic ratio (all $P<0.05$). Thus, serum miRNA-126 levels could serve as a potential candidate biomarker for evaluating the severity of AF and HF.

miRNA-150

In a study performed by McManus,[66] plasma levels of miRNA-150, known to influence atrial fibrosis and pro-fibrillatory potential under experimental conditions, were

2-fold lower among patients with AF than among those without AF. In addition, plasma level of miRNA-150 also was lower in participants with persistent AF than in those with paroxysmal AF and increased 3-fold after AF ablation. Goren et al.[67] found that miRNA-150 expression was 3.2-fold lower in platelets of HF patients with AF, relative to those without AF. A similar effect was seen in serum samples from the same patients, in which miRNA-150 levels were 1.5-fold lower (P=0.004) in HF patients with AF. Thus, the authors concluded that miRNA-150 expression levels in platelets of patients with systolic HF with AF are significantly reduced and correlated to the cell-free circulating levels of this miRNA.

miRNA-483

miRNA-483-5p, typically transcribed with its host gene, *IGF2*, has been isolated in several human tissue types including myocardium, hepatic and brain tissue as well as in blood serum.[68,69] Harling et al.[70] found significant overexpression of miRNA-483-5p in the pre-operative serum of patients with postoperative AF. It is possible that the observed increase in miRNA-483-5p expression represents upregulation of the *IGF2* gene, which, for example, may be stimulated in states of cardiac stress. Overexpression of *IGF2* may also play a role in providing a pro-inflammatory substrate through the regulation of NF-kB- and IL-6-mediated pathways, which may in turn lower the threshold on which a surgical trigger may potentiate AF in the postoperative period.[71]

Remodeling of the autonomic nervous system in AF mediated by miRNAs

ANS has been shown to have an important role in the initiation and maintenance of AF.[72] Activation of either the extrinsic parasympathetic or sympathetic neural elements of the cardiac ANS has been reported to induce rapid focal firing and AF induction via mechanisms of shortening the atrial or pulmonary vein refractoriness mediated by parasympathetic neurotransmitters or increasing intracellular Ca2+ concentrations mediated by sympathetic neurotransmitters, respectively. These results indicate the complexity and multiple functions of the cardiac ANS in inducing AF.[73]

Rao et al.,[74] utilizing the right cervical vagus trunk stimulation (RVTS) to successfully induce AF by reducing the effective refractory period (ERP) and increasing dERP, hypothesized that RVTS activates the extrinsic and/or intrinsic cardiac ANS to mediate neural remodeling, which initiates and/or maintains AF, presumably by increasing the activity of acetylcholine. Modulation of ANS activity may constitute an important therapeutic strategy for the management of atrial tachyarrhythmias.[75]

At least two miRNAs, miRNA-30 and miRNA-206, are involved in the ANS remodeling in AF.

miRNA-30

Among 355 of 1,205 human miRNAs being expressed and assumed functioning in the heart, miRNA-30d is the sixth most abundantly expressed miRNA, which indicates that it could be a crucial regulator of cardiomyocytes in the physiological and/or pathophysiological condition. Morishima et al.[76] demonstrated a novel role for miRNA-30d in remodeling the cardiac ion channel in human persistent AF. miRNA-30d was upregulated, whereas *KCNJ3*, a target gene of miRNA-30d, was downregulated in human AF cardiomyocytes. The authors provided the first evidence that the downward remodeling of IK.ACh in Ca2+-overloaded cardiomyocytes is attributed, at least in part, to deranged Ca2+ handling, leading to the upregulation of miRNA-30d in human AF.

miRNA-206

Cardiac autonomic nerve remodeling (ANR) is a critical mechanism in AF. Zhang et al.[77] performed a study to assess the underlying role of miRNAs in regulating cardiac ANR in AF by right atrial tachypacing (A-TP) in dogs. Forced expression of miRNA-206 through lentiviral infection based on A-TP *in vivo* significantly shortened the atrial ERP. The regeneration of nerves increased more than 2-fold by miRNA-206 overexpression. The expression of SOD1 was repressed by miRNA-206 overexpression, indicating SOD1 as a direct target of miRNA-206. Overexpression of miRNA-206 increased reactive oxygen species (ROS) levels *in vitro* and *in vivo*. Thus, overexpression of miRNA-206 promoted ANR by targeting SOD1 and production of ROS.

It was also reported that miRNA-206 overexpression in an experimental canine model inhibited expression of the *GCH1* gene, which encodes GTP cyclohydrolase I, a key enzyme in *de novo* synthesis of tetrahydrobiopterin (BH4), an essential cofactor for NO synthesis.[78] Previous studies reported that increased tetrahydrobiopterin (BH4) and NO content negatively regulated nerve regeneration. These findings suggested that *GCH1* downregulation exacerbates ANR by decreasing atrial BH4 and NO content modulated by miRNA-206 in A-TP canines.

Dysregulation of Ca2+ level in AF mediated by miRNAs

Calcium plays a fundamental role in the pathophysiology of AF. Enhanced SR Ca(2+) leak through ryanodine receptor type-2 (RyR2), in combination with larger I(NCX) for a given (SR) Ca(2+) release and increased diastolic [Ca(2+)](i)-voltage coupling gain, causes AF-promoting atrial delayed afterdepolarizations/triggered activity in AF patients.[79] The rise in intracellular calcium concentrations also activates pro-fibrotic pathways leading to SR in the atria that produces a substrate that can support the complex re-entry seen in AF.[80] Ca(2+)-related miRNAs have been found to be significant pathophysiological contributors in conditions like myocardial ischemic injury, cardiac hypertrophy, heart failure, ventricular arrhythmogenesis, and AF.[81]

miRNA-106

Recent studies have shown that the level of RyR2 protein is elevated in atria of patients with paroxysmal AF, suggesting that miRNA-mediated post-transcriptional regulation of RyR2 might be an underlying mechanism. Bioinformatic analysis suggests that miRNA-106b, a member of the miRNA-106b-25 cluster, could bind to RyR2-3'-untranslated region and suppress its translation. Quantitative real-time PCR showed that the level of mature miRNA-106b was lower in atria of patients with paroxysmal AF than in patients in sinus rhythm. Ca(2+)-spark frequency and total sarcoplasmic reticulum Ca(2+)-leak were increased in atrial myocytes of miRNA-106b-25(-/-) mice, and these mice exhibited more frequent atrial ectopy and were also more susceptible to pacing-induced AF than wild-type littermates.[82]

miRNA-208

Results from analysis of miRNA-208b-overexpressing HL-1 atrial myocytes and from myocytes isolated from CAF patients showed that aberrant miRNA-208b levels reduced the expression and function of L-type Ca2+ channel subunits (CACNA1C and CACNB2) as well as the sarcoplasmic reticulum-Ca2+ pump SERCA2.[83]

The above data on the role of miRNAs in the pathophysiology of AF and the possibility of being used as AF biomarkers are summarized in Table 1.

miRNAs as AF biomarkers

miRNA expression in tissue and blood can be used as a biomarker for various diseases. A biomarker has been defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic process, or pharmacologic responses to a therapeutic intervention"[84] and "A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions."[85]

Currently, there are no suitable biomarkers for the primary diagnosis of AF. The use of natriuretic peptides and troponins, which are of very high value in myocardial infarction and HF, is ineffective with regard to the diagnosis and prognosis of AF.[6] High stability, sensitivity, specificity, and prognostic properties of c-miRNAs make them an attractive biomarker for the early diagnosis of numerous diseases, including CVD.[86] Moreover, miRNA expression can be detected both in biological fluids (plasma, serum), and in individual heart tissues and blood cells.

c-miRNAs exhibit numerous essential characteristics of biomarkers: While they are extremely stable in circulation, their expression is tissue-/disease-specific, and they can be easily detected using sequence-specific amplification methods. These features of c-miRNAs are helpful in the development of non-invasive assays to monitor the progress of CVDs.[87,88]

Studies performed by Natsume et al.[88] revealed that four miRNAs (miRNA-99a-5p, miRNA-192-5p, miRNA-214-3p, and miRNA-342-5p) were significantly upregulated in AF patients. A receiver-operating characteristics curve indicated that miRNA-214-3p and miRNA-342-5p had the highest accuracy. The combination of the four miRNAs modestly improved the predictive accuracy for AF (76% sensitivity, 80% specificity).

c-miRNAs might be potential biomarkers of AF. They are easily accessible, relatively stable and in some instances tissue specific. At the least, c-miRNAs may offer new insights into the mechanisms of AF.[89] Further studies are required to gain a better understanding of the role of miRNAs in the pathophysiology of AF, which will provide tremendous opportunities for targeted therapy of AF in the near future.

Table 1.

The role of miRNAs in the pathophysiology of AF and the possibility of being used as AF biomarkers

Pathophysiological mechanism	miRNA	Targets and effects	A relationship of the elevated/ decreased levels of miRNAs with AF	Source
Electrical remodeling	miRNA-1	Downregulation of the expression of the KCNE1, KCNB2 HCN2, and HCN4 genes	Both increased and decreased miRNA-1 expression may be associated with AF	[42-45]
	miRNA-328	Downregulation of the expression of the CACNA1C and CACNB1 genes	An increased miRNA-328 expression is associated with AF	[48-50]
	miRNA-499	Downregulation of the expression of the KCNN3 and CACNB2 genes	An increased miRNA-499 expression is associated with AF	[51-53]
Structural remodeling	miRNA-21	Downregulation of the expression of the CACNA1C and CACNB2 mRNAs	An increased miRNA-21 expression is associated with AF	[56-58]
	miRNA-29	Downregulation of the expression of the COL1A1, COL3A1, and FBN1 genes	Down-expression of miRNA-29 is associated with AF	[62, 63]
	miRNA-126	Downregulation of the EGFL7 expression	Down-expression of miRNA-126 is associated with AF	[64,65]
	miRNA-483	Upregulation of the expression of the IGF2 gene	An increased miRNA-483 expression is associated with AF	[70]
Remodeling of ANS	miRNA-30	Downregulation of the expression of IKACh gene	An increased miRNA-30 expression is associated with AF	[76]
	miRNA-206	Downregulation of the expression of the SOD1 и GCH1 genes	An increased miRNA-206 expression is associated with AF	[77,78]
Dysregulation of Ca2+ level	miRNA-106	Downregulation of the expression of the RYR2 gene	Down-expression of miRNA-106 is associated with AF	[82]
	miRNA-208	Downregulation of the expression of the SERCA2a, CACNA1C, and CACNB2 genes	An increased miRNA-208 expression is associated with AF	[83]

Competing Interests

The authors declare that they have no competing interests.

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