УДК 616.12-008.313.2:577.21
https://doi.org/10.20538/1682-0363-2021-3-203-212

MicroRNA: the role in the pathophysiology of atrial fibrillation and potential use as a biomarker

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ABSTRACT

The aim of the study was to analyze medical literature on the role of microRNA in the pathophysiology of atrial fibrillation and the possibilities of using microRNAs as biomarkers.

The analysis of modern medical literature was carried out using the PubMed – NCBI database.

Atrial fibrillation (AF) is a common and serious cardiovascular disease. The pathophysiological mechanisms underlying the development of atrial fibrillation are not entirely clear. In addition, there are no optimal biomarkers for early detection and assessment of the prognosis for patients with atrial fibrillation. Recently, the attention of researchers has been directed to the molecules of microRNA. There is a lot of evidence that they are involved in the pathogenesis of neurological, oncological, and cardiovascular diseases. This review examines the role of microRNAs in the pathophysiology of atrial fibrillation. The possibility of using microRNA as a biomarker for the diagnosis and prediction of atrial fibrillation is also discussed.

MicroRNAs play a crucial role in the pathophysiology of atrial fibrillation, regulating the mechanisms of atrial remodeling, such as electrical remodeling, structural remodeling, remodeling of the autonomic nervous system, and impaired regulation of calcium levels. The stability of microRNAs and the possibility to study them in various biological fluids and tissues, including blood, make these molecules a promising diagnostic biomarker for various cardiovascular diseases. The presented data clearly indicate that AF is associated with changes in the expression level of various microRNAs, which can be quantified using a polymerase chain reaction. Further research is required to assess the role of microRNAs as biomarkers for atrial fibrillation, in particular to establish precise reference limits.

Key words: microRNA, atrial fibrillation, pathophysiology, biomarker, laboratory diagnostics.

Conflict of interest. The authors declare the absence of obvious or potential conflicts of interest related to the publication of this article.

Source of financing. The authors state that they received no funding for the study.

For citation: Chaulin A.M., Duplyakov D.V. MicroRNA: the role in the pathophysiology of atrial fibrillation and potential use as a biomarker. *Bulletin of Siberian Medicine.* 2021; 20 (3): 203–212. https://doi.org/10.20538/1682-0363-2021-3-203-212.

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МикроРНК: роль в патофизиологии фибрилляции предсердий и возможности использования в качестве биомаркера

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РЕЗЮМЕ

Проведен анализ современной медицинской литературы по базе данных PubMed – NCBI. Фибрилляция предсердий является широко распространенным и серьезным сердечно-сосудистым заболеванием. Патофизиологические механизмы, лежащие в основе развития фибрилляции предсердий, не совсем ясны. Кроме того, отсутствуют оптимальные биомаркеры для раннего выявления и оценки прогноза пациентов с фибрилляцией предсердий.

В последнее время внимание исследователей привлекли молекулы микрорибонуклеиновой кислоты (микроРНК). Накоплено немало данных, согласно которым они участвует в патогенезе неврологических, онкологических и сердечно-сосудистых заболеваний. Рассмотрена роль микроРНК в патофизиологии фибрилляции предсердий. Также обсуждается возможность использования микроРНК в качестве биомаркеров для диагностики и прогнозирования фибрилляции предсердий.

Ключевые слова: микроРНК, фибрилляция предсердий, патофизиология, биомаркер, лабораторная диагностика.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

Для цитирования: Чаулин А.М., Дупляков Д.В. МикроРНК: роль в патофизиологии фибрилляции предсердий и возможности использования в качестве биомаркера. *Бюллетень сибирской медицины.* 2021; 20 (3): 203–212. https://doi.org/10.20538/1682-0363-2021-3-203-212.

INTRODUCTION

Atrial fibrillation (AF) is the most common and persistent type of cardiac arrhythmia. The most common risk factors for AF are heart failure, diabetes, hypertension, hyperthyroidism, obesity, gender, and the presence of structural heart diseases [1].

Many risk factors for AF, including genetic, molecular, and environmental ones, contribute to the development of other cardiovascular diseases (CVD) [2]. According to the latest data, there are more than 33 million people with AF worldwide. It is worth noting that the incidence is characterized by gender peculiarities – in men, the frequency of AF is 3 times higher than in women [3].

The simplest and most commonly used method for diagnosing AF is electrocardiography (ECG), but this method has a significant drawback that consists in short duration of recording of the electrical activity of the heart, which limits the diagnosis in asymptomatic patients [4]. Existing laboratory biomarkers of myocardial damage (cardiac troponins, natriuretic peptides, creatine phosphokinase (CPK), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), etc.) are of little importance for predicting the course of AF [5–7]. The increase in cardiac troponins in AF occurs due to damage to cardiomyocytes, which is provoked by a decrease in the blood supply to the myocardium. It is believed that insufficient blood supply to the myocardium in AF occurs following shortening of the myocardial relaxation phase (diastole) [7]. According to some data, troponins correlate well with the severity of arrhythmia and can be used as prognostic markers [8], while according to other data, they are ineffective [9]. Therefore, there is a need to search for new and more reliable biomarkers for early diagnosis of AF.

Recently, due to the discovery of new regulatory molecules, the genetic component has been considered as a significant risk factor for the development of AF [10, 11]. MicroRNAs (miRNAs) were first dis-

covered in 1993 by a group of researchers under the guidance of R. Lee in a free-living nematode Caenorhabditis elegans [12]. MiRNAs are single-stranded ribonucleic acids that do not encode protein and consist of about 22 nucleotides [13]. According to a number of studies, miRNAs play a vital role in various developmental processes in animals and humans, including growth, proliferation, differentiation, and cell metabolism [14]. In mammals, about 2,200 different miRNAs have been found, that regulate about one third of protein-encoding genes [15]. It was reported that changes in miRNA expression are associated with various pathological conditions, such as neurological diseases, autoimmune disorders, cardiovascular diseases, and cancer. For example, a change in the character of miRNA expression can promote transformation of healthy cells into malignant ones [16].

The process of cardiac remodeling was associated with changes in the expression of miRNA in the heart tissue and blood, while miRNA levels had prognostic and diagnostic value [17–19]. It was also reported that modulation of miRNA expression decreases or increases susceptibility to the development of AF in vivo. Therefore, miRNAs can be a potential target for the effects of therapeutic agents used to treat AF [20]. Understanding the pathophysiological mechanisms regulated by miRNAs is essential for improving diagnostic and treatment strategies in AF.

ROLE OF MiRNA IN THE PATHOPHYSIOLOGY OF AF

According to recent data, miRNAs play a crucial role in the pathophysiology of AF, regulating the mechanisms of atrial remodeling. The decrease and increase in the miRNA expression are genetically programmed and, under normal conditions, contribute to the development of the cardiovascular system in humans and animals. At the same time, changes in the level of miRNA expression in circulating blood and tissues can also occur in pathological conditions associated with the development of various CVDs, including AF, which lead to myocardial remodeling.

To date, due to numerous experimental and clinical studies, information on the role of miRNAs in the pathogenesis of AF has been accumulated. The following key pathogenetic mechanisms in the initiation and progression of AF can be distinguished, in the regulation of which miRNAs are involved: electrical remodeling, structural remodeling, remodeling of the cardiac autonomic nervous system, and impaired intracellular homeostasis of calcium ions (Ca2 +). The major part of this review article is devoted to consistent discussion of the role of miRNAs in each of these mechanisms.

MiRNA-mediated electrical remodeling in AF

Electrical remodeling of cardiomyocytes is the most common change associated with AF. Electrical remodeling occurs due to a decrease in the L-type calcium channel conductance (ICaL) and an increase in the inward rectifier potassium channel conductance (IK1). Changes in the electrical properties of Ca2 +-dependent potassium channels and connexin 40 and connexin 43 gap junction ion channels also induce electrical remodeling associated with AF [21]. Several different miRNAs are involved in the process of electrical remodeling: miRNA-1, miRNA-328, and miRNA-499, each of which exhibits several specific properties.

MiRNA-1 is abundantly expressed in cardiac and skeletal muscles and plays an important role in the embryogenesis (development) of muscle tissue. It was found that miRNA-1 promotes differentiation and proliferation of myoblasts [22]. Changes in the expression of miRNA-1 affect the electrophysiology of the heart, increasing the risk of developing cardiac arrhythmia. Thus, a study of atrial tachycardia on a rabbit model showed that overexpression of miRNA-1 shortens the atrial effective refractory period induced by tachycardia and increases the inward rectifier potassium channel current (IKs) by reducing the expression of *KCNE1* and *KCNB2* genes encoding potassium channel subunits. Knockdown (inactivation) of miRNA-1, on the contrary, weakens the suppression of *KCNE1* and *KCNB2* genes, shortens the atrial effective refractory period, and increases IKs. Thus, it was found that *KCNE1* and *KCNB2* are target genes for miRNA-1. It was also suggested that targeted suppression of these potassium channel genes enhances the duration and incidence of AF. Therefore, the study demonstrated the crucial role of miRNA-1 in electrical remodeling and its clinical significance as a potential therapeutic target for AF [23]. Another study examined the expression of cardiac muscle-specific miRNAs, including miRNA-1, in the right atrium of postoperative patients. It was found that after coronary artery bypass grafting, the expression of miRNA-1 in the myocardial tissue of the right atrium increased and it contributed to postoperative apoptosis of cardiomyocytes and played an essential role in the development of postoperative AF. Postoperative AF is a serious complication of cardiac surgery which

is associated with poor prognosis. However, there were no differences in the level of miRNA-1 in the blood plasma of patients with postoperative AF and patients with normal sinus rhythm or without AF in the medical history [24]. Some studies have shown that miRNA-1 expression is lower in elderly patients with AF than in younger patients with normal sinus rhythm. A decrease in the expression of miRNA-1 leads to the activation of transcription of *HCN2* and *HCN4* – genes encoding cyclic nucleotide-gated channels activated by hyperpolarization. Therefore, it was found that with age the expression of miRNA-1 decreases; while the expression of *HCN2* and *HCN4*, on the contrary, increases, and these alterations contribute to electrophysiological changes, increasing the likelihood of AF development [25]. In patients with persistent AF, a decrease in the expression of miRNA-1, an increase in the expression of Kir2.1 potassium channel subunits, and a corresponding increase in IK1 conductance were observed. This leads to a slowdown in cardiac conduction and increases the risk of AF induction [26]. A number of studies confirm the relationship between the expression of miRNA-1 and the emergence of arrhythmia [25–28]. In particular, miRNA-1 was shown to modulate electrical remodeling of the heart by decreasing the concentration of intracellular calcium ions, which ultimately reduce the expression of *CACNB2* [27]. In addition, downregulation of Ca2 + regulatory proteins, such as calmodulin (CaM), protein phosphatase 2A (PP2A), Na + / Ca2 + exchanger (NCX), and phospholamban (PLN), contributes to the pathogenesis of AF by shortening the atrial effective refractory period [28].

MiRNA-328 is also involved in atrial remodeling. In a study by Y. Lu et al., it was shown that the expression level of miRNA-328 in the atrial myocardium in animals and patients with AF was several times higher than in the controls [29]. Activation of miRNA-328 decreases the expression of the *CACNA1C* and *CACNB1* genes encoding the L-type calcium channel subunits, which leads to a decrease in ICaL and, as a consequence, reduces the action potential duration, that predisposes to the development of AF [29, 30]. Another study reported that the level of miRNA-328 in the blood plasma of patients with AF was higher than in the controls. It is worth noting that the expression level of miRNA-328 in patients with AF also differed depending on the site of blood collection. Thus, the level of miRNA-328 in the blood plasma collected from the left atrial appendage was higher than that in the peripheral blood and blood obtained from the pulmonary vein [31]. The authors of this work suggested that the localized expression of miRNA-328 in the left atrium may be involved in the process of cardiac remodeling in patients with AF.

MiRNA-499. A comparative study of patients with permanent AF and patients with normal sinus rhythm showed that activation of miRNA-499 significantly suppressed the expression of cardiac *SK3* (small conductance calcium-activated potassium channel 3) by targeting the *KCNN3* gene [32]. It was reported that miRNA-499 lowers the expression of the *CACNB2* gene encoding the L-type calcium channel subunit, which contributes to the development of AF [33]. The expression of miRNA-499 in patients with AF with rapid ventricular rate was 2.3 times higher than in AF patients with slow ventricular response and in patients from the control group [34].

MiRNA-mediated structural remodeling in AF

MiRNAs that are involved in structural remodeling regulate protein-encoding genes responsible for the formation of the extracellular matrix and promote atrial fibrosis by regulating pro- and antifibrotic signaling pathways [35]. These miRNAs are mainly involved in reducing the conduction rate and increasing the reentrant activity [36]. The following miRNAs are involved in the structural remodeling of the heart in AF: miRNA-21, miRNA-29, miRNA-126, miRNA-150, and miRNA-483.

MiRNA-21. The expression of miRNA-21 is increased in cardiomyocytes in patients with persistent AF [37]. This causes a decrease in the expression of *CACNA1C* and *CACNB2* genes, encoding two subunits of voltage-gated calcium channels, which leads to a decrease in ICaL [37]. Elevated expression of miRNA-21 in fibroblasts increases the risk of cardiac fibrosis and associated AF. According to O. Adam et al., elevated expression of miRNA-21 in the myocardium of rats and humans with AF increases the activity of mitogen-activated protein kinase / extracellular signal-regulated kinases (MAPK / ERK signaling pathway), which promotes atrial remodeling and fibrosis [38]. Administration of a miRNA-21 antagonist in vivo potentially reduces atrial fibrosis and the risk of AF [39]. In addition, increased expression of miRNA-21 promotes atrial remodeling in an experimental rat model by activating phosphoinositide 3-kinase (PI3K), which leads to inhibition of *PTEN* gene expression [40]. Therefore, suppression of signaling pathways associated with miRNA-21 may be a new approach to AF therapy [39, 40].

MiRNA-29 plays a crucial role in the remodeling of extracellular matrix proteins [41] by regulating the *COL1A1, COL3A1*, and *FBN1* genes encoding collagen 1A1, collagen 3A1, and fibrillin. The level of miRNA-29 in the plasma of patients with AF and patients simultaneously suffering from chronic heart failure and AF is significantly lower than in the control group. In mice, adenovirus-mediated inhibition of miRNA-29 markedly increases the expression of *COL1A1* miRNA and collagen content in the cardiac tissue, which indicates a potential role of miRNA-29 in fibrotic remodeling [42].

MiRNA-126 is involved in the angiogenesis by regulating the expression of epidermal growth factor-like domain 7 (EGFL7). It was shown that miRNA-126 is abundantly expressed in the human heart and detected in significant amounts in the blood serum [43]. The level of miRNA-126 in AF patients is noticeably lower than in the controls. In addition, the level of miRNA-126 in patients with heart failure and AF is significantly lower than in patients suffering only from heart failure or in patients only with AF. The expression of miRNA-126 positively correlated with the left ventricular ejection fraction ($r = 0.374$, $p < 0.01$) and negatively correlated with the level of the N-terminal brain natriuretic propeptide ($r = –0.783$, $p < 0.01$). This indicates a relationship between the level of miRNA-126 in the blood serum and the severity of the disease [44].

MiRNA-150 plays an essential role in the pathogenesis of AF. The expression of miRNA-150 was low in platelets and serum of patients with chronic systolic heart failure with or without AF. The expression level of miRNA-150 in platelets of patients with AF was 3.2 times lower than in platelets of the controls. Likewise, the serum miRNA-150 level in patients with AF was 1.5 times lower than in patients with heart failure, but without AF. In addition, serum miRNA-150 levels closely correlated with platelet miRNA-150 levels ($r = 0.65$, $p = 0.0087$). The researchers suggested that a lower level of miRNA-150 in platelets may promote their activation and contribute to a prothrombotic state in AF [45]. A prospective study investigated the expression of miRNA-150 in blood plasma and atrial tissue of patients with and without AF and in patients undergoing cardiac ablation. Plasma miRNA-150 levels in AF patients were 2 times lower than in the controls. In addition, the plasma miRNA-150 level in patients with paroxysmal atrial fibrillation was lower than in patients with persistent AF. The expression level of miRNA-150 one month after AF ablation was 3 times higher than before the surgery [46]. According to Z. Liu et al., a decrease in the miRNA-150 level in patients with AF was associated with an increase in the expression of inflammatory cytokines and mediators, such as interleukin (*IL*-6), *IL*-18, tumor necrosis factor alpha (TNF-a), transforming growth factor beta (TGF-β), and C-reactive protein (CRP). In patients with AF, miRNA-150 levels closely correlated with CRP ($r = 0.77$) [18].

MiRNA-483. The level of circulating miRNA-483 in the blood may be a potential biomarker of the risk of AF in postoperative patients [47]. It was found that activation of transcription of the *IGF2* gene encoding the insulin-like growth factor is the result of miRNA-483 overexpression. This, in turn, enhances the expression of proinflammatory mediators by regulating pathways mediated by *IL-6* and nuclear factor kappa B (NF-kB). In patients with higher miRNA-483 expression in the serum prior to coronary artery bypass grafting, the risk of postoperative AF was higher [47]. This suggests that miRNA-483 may be a potential biomarker for predicting early development of postoperative AF.

MiRNA-mediated remodeling of the cardiac autonomic nervous system in AF

It is known that changes in the electrical activity of the heart are closely related to the stimulation of the vagus nerve and release of acetylcholine, which leads to shortened duration of the action potential, contributing to the progression of AF [48]. Modulation of the activity of the autonomic nervous system is a very valuable and promising strategy in the treatment of atrial arrhythmia. It was shown that at least two miRNAs, miRNA-30 and miRNA-206, are involved in the remodeling of the cardiac autonomic nervous system in AF.

MiRNA-30. Dysregulation of the cardiac autonomic nervous system mediated by miRNA-30 plays a fundamental role in the initiation and maintenance of AF by increasing the current through G-protein-gated inwardly rectifying potassium channels (IKACh), which decreases the duration of the action potential [49]. An increase in the miRNA-30 expression caused inhibition of the *KCNJ3* gene expression and a decrease in acetylcholine-activated K^+ current (IK^+, ACh) in patients with persistent AF [50].

MiRNA-206. In vitro and in vivo experiments have shown that overexpression of miRNA-206 in the autonomic ganglia suppresses the expression of the *SOD1* gene encoding superoxide dismutase, the enzyme of

the antioxidant defense, which leads to an increase in the formation of reactive oxygen species and shortening of the effective refractory period in the atria [51]. This study confirmed the relationship between the overproduction of reactive oxygen species and increased predisposition to AF. It was also reported that an increase in the expression of miRNA-206 in an experimental dog model suppressed the *GCH1* gene encoding GTP cyclohydrolase I, a key enzyme in the de novo synthesis of tetrahydrobiopterin, which is a coenzyme for nitric oxide synthesis. A decrease in the levels of tetrahydrobiopterin and nitric oxide in the atria was accompanied by reduction of the effective refractory period and contributed to the development of AF. On the contrary, overexpression of the *GCH1* gene prevented the development of AF [52]. Therefore, in this study, it was shown that miRNA-206-mediated inhibition of the *GCH1* gene promotes the onset of AF. Further investigation of this mechanism is a promising direction for development of therapy.

MiRNA-MEDIATED IMPAIRMENT OF INTRACELLULAR HOMEOSTASIS OF CA^{2+} IONS IN AF

Changes in miRNA expression in the heart affect the homeostasis of Ca^{2+} ions in cardiomyocytes, leading to delayed afterdepolarization [53]. Delayed afterdepolarization is the result of increased release of diastolic Ca^{2+} from the sarcoplasmic reticulum through the ryanodine receptor 2 (RYR2) and promotes the release of Ca^{2+} through the sodium-calcium exchanger (NCX) [54]. Impaired regulation of intracellular homeostasis of Ca^{2+} ions is mediated by several miRNAs, such as miRNA-106 and miRNA-208.

MiRNA-106. In an experimental study, it was shown that miRNA-106 suppresses the translation (biosynthesis) of RYR2, while a decrease in the expression of miRNA-106, observed in the atrial myocardium during AF, activates the expression of RYR2, which increases the release of Ca^{2+} from the sarcoplasmic reticulum, contributing to the pathogenesis of AF. Thus, in mice with knocked out miRNA-106, a spontaneous increase in Ca^{2+} release through RYR2 was observed, which caused an increased incidence of ectopic atrial rhythm and AF [55].

MiRNA-208. It was shown that miRNA-208 plays an important role in the regulation of calcium levels. An increase in the expression of miRNA-208 in atrial myocytes obtained from patients with AF is associated with a decrease in the expression of Ca-ATPase (SERCA2a) in the sarcoplasmic reticulum, which is necessary for the transport of Ca^{2+} ions from the cytosol to the sarcoplasmic reticulum. In addition, increased levels of miRNA-208 reduce the expression of L-type calcium channel subunits (CACNA1C and CACNB2) [56].

The above stated data on the role of miRNAs in the pathophysiology of AF and the possibility of their use as biomarkers are summarized in the Table.

Table

The role of miRNAs in the pathophysiology of AF and the possibility of their use as biomarkers

Pathophysiological mechanism	miRNA	Targets and effects	Association between increased / decreased levels of miRNA with AF	Reference
Electrical remodeling	miRNA-1	Decrease in the expression of *KCNE1* and *KCNB2, HCN2, HCN4*	Both increase and decrease in miRNA-1 levels may be associated with AF.	[23–26]
	miRNA-328	Decrease in the expression of *CACNA1C* and *CACNB1*	Elevated miRNA-328 levels are associated with AF	[29–31]
	miRNA-499	Decrease in the expression of *KCNN3* and *CACNB2*	Increased miRNA-499 levels are associated with AF	[32–34]
Structural remodeling	miRNA-21	Decrease in the expression of *CACNA1C, CACNB2, PTEN*	Increased miRNA-21 levels are associated with AF	[37–40]
	miRNA-29	Decrease in the expression of *COL1A1, COL3A1, FBN1*	Decreased miRNA-29 levels are associated with AF	[41, 42]
	miRNA-126	Decrease in the expression of *EGFL7*	Decreased miRNA-126 levels are associated with AF	[43, 44]
	miRNA-150	Decrease in the expression of *IL*-6, *IL*-18, TNFα, TGFβ, CRP	Decreased miRNA-150 levels are associated with AF	[18, 45]
	miRNA-483	Increase in the expression of *IGF2*	Increased miRNA-483 levels are associated with AF	[47]
Remodeling of the autonomic nervous system	miRNA-30	Decrease in the expression of *KCNJ3*	Increased miRNA-30 levels are associated with AF	[50]
	miRNA-206	Decrease in the expression of *SOD1* and *GCH1*	Increased miRNA-206 levels are associated with AF	[51, 52]
Impaired regulation of calcium levels	miRNA-106	Decrease in the expression of *RYR2*	Decreased miRNA-106 levels are associated with AF	[55]
	miRNA-208	Decrease in the expression of *SERCA2a, CACNA1C, CACNB2*	Increased miRNA-208 levels are associated with AF	[56]

MiRNAs AS BIOMARKERS OF AF

The expression of miRNA in tissues and blood can be used as a biomarker in various diseases. According to the National Institutes of Health (NIH) and the World Health Organization (WHO), a biomarker is a biological molecule or its products that can be measured in blood, tissue, or other body fluids as an indicator of normal and abnormal body functioning or that can predict morbidity. Currently, there are no suitable biomarkers for primary diagnosis of AF. The use of natriuretic peptides and cardiac troponins, which are significant in a number of cardiovascular diseases (myocardial infarction, heart failure, etc.), is ineffective in the diagnosis and prognosis of AF [6]. At the same time, high stability, sensitivity, specificity, and prognostic properties of circulating miRNAs make them attractive biomarkers for early diagnosis of numerous diseases, including AF [57].

MiRNAs are very stable under extreme conditions, such as changes in acidity (pH) and high or low temperatures, and can withstand multiple freeze-thaw cycles. MiRNAs can be easily detected with high specificity and sensitivity in serum and plasma using a polymerase chain reaction [58]. Since miRNAs are bound to high-density lipoproteins or incorporated into microvesicles, exosomes, and apoptotic bodies, they are resistant to RNase activity. However, exogenous miRNAs are rapidly degraded by RNase in the plasma. The stability of miRNAs and the possibility of their detection in many biological fluids make them promising biomarkers for many CVDs, including AF [59, 60].

Numerous studies have shown that certain types of miRNAs responsible for gene regulation and heart remodeling, in particular miRNA-1 [24–28], miRNA-328 [29–31], miRNA-499 [32–34], miRNA-21 [37-40], miRNA-150 [45, 46], and a number of others (Table), may become a new class of diagnostic and prognostic biomarkers for AF.

CONCLUSION

By influencing the electrical and structural remodeling of the atria, remodeling of the autonomic nervous system of the heart and impaired homeostasis of intracellular calcium, miRNAs create the prerequisites for the emergence of atrial fibrillation (AF). Stability of miRNAs and a possibility to study them in various biological fluids and tissues, including blood, make them promising diagnostic biomarkers for AF. Further studies are required to assess the role of miRNAs as new biomarkers of AF development.

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Received 26.05.2020
Accepted 29.09.2020